

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number
WO 01/16318 A2

(51) International Patent Classification ⁷ :	C12N 15/12, C07K 14/47, 14/705, G01N 33/53, C12N 15/62, C07K 16/18	PCT/US00/04414	22 February 2000 (22.02.2000)	US
		PCT/US00/05601	1 March 2000 (01.03.2000)	US
	60/187,202		3 March 2000 (03.03.2000)	US
(21) International Application Number:	PCT/US00/23328	60/191,007	21 March 2000 (21.03.2000)	US
(22) International Filing Date:	24 August 2000 (24.08.2000)	PCT/US00/08439	30 March 2000 (30.03.2000)	US
(25) Filing Language:	English	60/199,397	25 April 2000 (25.04.2000)	US
(26) Publication Language:	English	PCT/US00/14042	22 May 2000 (22.05.2000)	US
(30) Priority Data:	PCT/US99/20111	60/209,832	5 June 2000 (05.06.2000)	US
	1 September 1999 (01.09.1999) US	(71) Applicant (for all designated States except US): GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).		
PCT/US99/21090	15 September 1999 (15.09.1999) US	(72) Inventors; and		
60/169,495	7 December 1999 (07.12.1999) US	(75) Inventors/Applicants (for US only): EATON, Dan, L. [US/US]; 75 Knight Drive, San Rafael, CA 94901 (US). FILVAROFF, Ellen [US/US]; 538 18th Avenue, San Francisco, CA 94121 (US). GERRITSEN, Mary, E. [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). GODOWSKI, Paul, J. [US/US]; 2627 Easton Drive, Burlingame, CA 94010 (US). GRIMALDI, Christopher, J. [US/US]; 1434 36th		
60/170,262	9 December 1999 (09.12.1999) US			
60/175,481	11 January 2000 (11.01.2000) US			
PCT/US00/04341	18 February 2000 (18.02.2000) US			
PCT/US00/04342	18 February 2000 (18.02.2000) US			

[Continued on next page]

(54) Title: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

<subunit 1 of 1, 266 aa, 1 stop
<MW: 29766, pI: 8.39, NX(S/T): 0
MWWFQQGLSFLPSALVIWTSAAFIFSYITAVTLLHHIDPALPYISDTGTVAPEKCLFGAMLNIA.
AVLCIATIYVRYKQVHALSPEENVIKILNKAGLVLGILSCLGLSIVANFQKTTLFAAHVSGAV
LTFGMGSLYMFVQTILSYQMOPKIHGKQVFIRLLLVIWCGVSALSMLTCSSVLHSGNFGTDL
EQKLHWNPEDKGYVLHMITTAAEWSMSFSFFGLTYIRDFQKISLRVEANLHGLTLYDTAPC
PINNERTRLLSRDI

Important features:

Type II transmembrane domain:

amino acids 13-33

Other Transmembrane domains:

amino acids 54-73, 94-113, 160-180, 122-141

N-myristoylation sites.

amino acids 57-63, 95-101, 99-105, 124-130, 183-189

(57) Abstract: The present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

WO 01/16318 A2



Avenue, San Francisco, CA 94122 (US). GURNEY, Austin, L. [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). WATANABE, Colin, K. [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). WOOD, William, I. [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US).

(74) **Agents:** KRESNAK, Mark, T. et al.; Genentech, Inc., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- *Without international search report and to be republished upon receipt of that report.*
- *With (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE
SAME**

FIELD OF THE INVENTION

The present invention relates generally to the identification and isolation of novel DNA and to the
5 recombinant production of novel polypeptides.

BACKGROUND OF THE INVENTION

Extracellular proteins play important roles in, among other things, the formation, differentiation and
10 maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration,
differentiation, or interaction with other cells, is typically governed by information received from other cells
15 and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance,
mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which
are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted
20 polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of
action in the extracellular environment.

Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics,
biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons,
interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins.
Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts
25 are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are
focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel
secreted proteins. Examples of screening methods and techniques are described in the literature [see, for
example, Klein et al., *Proc. Natl. Acad. Sci.* 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

Membrane-bound proteins and receptors can play important roles in, among other things, the formation,
25 differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation,
migration, differentiation, or interaction with other cells, is typically governed by information received from
other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides
(for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and
hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins.
30 Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor
kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like
selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is
regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze
that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and

nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interactions. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

5 Efforts are being undertaken by both industry and academia to identify new, native receptor or membrane-bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor or membrane-bound proteins.

SUMMARY OF THE INVENTION

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, 5 the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid 10 sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% 15 nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively 20 at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain- 25 inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide 30 that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, 35 alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length,

WO 01/16318

alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, 5 alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700 nucleotides in length, alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel 10 fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide 15 molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid 20 sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid 25 sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid 30 sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

35 In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83%

amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By

way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

10 In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

15 In yet other embodiments, the present invention is directed to methods of using the PRO polypeptides of the present invention for a variety of uses based upon the functional biological assay data presented in the Examples below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO180 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA26843-1389".

20 Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence PRO218 cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA30867-1335".

25 Figure 4 shows the amino acid sequence (SEQ ID NO:4) derived from the coding sequence of SEQ ID NO:3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO263 cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA34431-1177".

30 Figure 6 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO295 cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA38268-1188".

35 Figure 8 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) of a native sequence PRO874 cDNA, wherein SEQ ID NO:9 is a clone designated herein as "DNA40621-1440".

Figure 10 shows the amino acid sequence (SEQ ID NO:10) derived from the coding sequence of SEQ ID NO:9 shown in Figure 9.

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a native sequence PRO300 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA40625-1189".

Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

5 Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO1864 cDNA, wherein SEQ ID NO:13 is a clone designated herein as "DNA45409-2511".

Figure 14 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence PRO1282 cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA45495-1550".

10 Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

Figure 17 shows a nucleotide sequence (SEQ ID NO:17) of a native sequence PRO1063 cDNA, wherein SEQ ID NO:17 is a clone designated herein as "DNA49820-1427".

15 Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ ID NO:17 shown in Figure 17.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO1773 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA56406-1704".

Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

20 Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO1013 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA56410-1414".

Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

25 Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO937 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA56436-1448".

Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence PRO842 cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA56855-1447".

30 Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO1180 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA56860-1510".

35 Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 27.

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO831 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA56862-1343".

WO 01/16318

Figure 30 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID NO:29 shown in Figure 29.

Figure 31 shows a nucleotide sequence (SEQ ID NO:31) of a native sequence PRO1115 cDNA, wherein SEQ ID NO:31 is a clone designated herein as "DNA56868-1478".

5 Figure 32 shows the amino acid sequence (SEQ ID NO:32) derived from the coding sequence of SEQ ID NO:31 shown in Figure 31.

Figure 33 shows a nucleotide sequence (SEQ ID NO:33) of a native sequence PRO1277 cDNA, wherein SEQ ID NO:33 is a clone designated herein as "DNA56869-1545".

10 Figure 34 shows the amino acid sequence (SEQ ID NO:34) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO1074 cDNA, wherein SEQ ID NO:35 is a clone designated herein as "DNA57704-1452".

Figure 36 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

15 Figure 37 shows a nucleotide sequence (SEQ ID NO:37) of a native sequence PRO1344 cDNA, wherein SEQ ID NO:37 is a clone designated herein as "DNA58723-1588".

Figure 38 shows the amino acid sequence (SEQ ID NO:38) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

Figure 39 shows a nucleotide sequence (SEQ ID NO:39) of a native sequence PRO1136 cDNA, wherein SEQ ID NO:39 is a clone designated herein as "DNA57827-1493".

20 Figure 40 shows the amino acid sequence (SEQ ID NO:40) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39.

Figure 41 shows a nucleotide sequence (SEQ ID NO:41) of a native sequence PRO1109 cDNA, wherein SEQ ID NO:41 is a clone designated herein as "DNA58737-1473".

25 Figure 42 shows the amino acid sequence (SEQ ID NO:42) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

Figure 43 shows a nucleotide sequence (SEQ ID NO:43) of a native sequence PRO1003 cDNA, wherein SEQ ID NO:43 is a clone designated herein as "DNA58846-1409".

Figure 44 shows the amino acid sequence (SEQ ID NO:44) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

30 Figure 45 shows a nucleotide sequence (SEQ ID NO:45) of a native sequence PRO1138 cDNA, wherein SEQ ID NO:45 is a clone designated herein as "DNA58850-1495".

Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

35 Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a native sequence PRO994 cDNA, wherein SEQ ID NO:47 is a clone designated herein as "DNA58855-1422".

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO1069 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA59211-1450".

Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO1411 cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA59212-1627".

Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a native sequence PRO1129 cDNA, wherein SEQ ID NO:53 is a clone designated herein as "DNA59213-1487".

Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a native sequence PRO1027 cDNA, wherein SEQ ID NO:55 is a clone designated herein as "DNA59605-1418".

Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ ID NO:55 shown in Figure 55.

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a native sequence PRO1106 cDNA, wherein SEQ ID NO:57 is a clone designated herein as "DNA59609-1470".

Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

Figure 59 shows a nucleotide sequence (SEQ ID NO:59) of a native sequence PRO1291 cDNA, wherein SEQ ID NO:59 is a clone designated herein as "DNA59610-1556".

Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ ID NO:59 shown in Figure 59.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO3573 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA59837-2545".

Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figure 61.

Figure 63 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO3566 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "DNA59844-2542".

Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a native sequence PRO1098 cDNA, wherein SEQ ID NO:65 is a clone designated herein as "DNA59854-1459".

Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a native sequence PRO1158 cDNA, wherein SEQ ID NO:67 is a clone designated herein as "DNA60625-1507".

WO 01/16318

Figure 68 shows the amino acid sequence (SEQ ID NO:68) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a native sequence PRO1124 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA60629-1481".

5 Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a native sequence PRO1287 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA61755-1554".

10 Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO1335 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "DNA62812-1594".

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

15 Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a native sequence PRO1315 cDNA, wherein SEQ ID NO:75 is a clone designated herein as "DNA62815-1576".

Figure 76 shows the amino acid sequence (SEQ ID NO:76) derived from the coding sequence of SEQ ID NO:75 shown in Figure 75.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a native sequence PRO1357 cDNA, wherein SEQ ID NO:77 is a clone designated herein as "DNA64881-1602".

20 Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) of a native sequence PRO1356 cDNA, wherein SEQ ID NO:79 is a clone designated herein as "DNA64886-1601".

25 Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ ID NO:79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) of a native sequence PRO1557 cDNA, wherein SEQ ID NO:81 is a clone designated herein as "DNA64902-1667".

Figure 82 shows the amino acid sequence (SEQ ID NO:82) derived from the coding sequence of SEQ ID NO:81 shown in Figure 81.

30 Figure 83 shows a nucleotide sequence (SEQ ID NO:83) of a native sequence PRO1347 cDNA, wherein SEQ ID NO:83 is a clone designated herein as "DNA64950-1590".

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID NO:83 shown in Figure 83.

35 Figure 85 shows a nucleotide sequence (SEQ ID NO:85) of a native sequence PRO1302 cDNA, wherein SEQ ID NO:85 is a clone designated herein as "DNA65403-1565".

Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:85 shown in Figure 85.

Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO1270 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA66308-1537".

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

5 Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO1268 cDNA, wherein SEQ ID NO:89 is a clone designated herein as "DNA66519-1535".

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

10 Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO1327 cDNA, wherein SEQ ID NO:91 is a clone designated herein as "DNA66521-1583".

Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO1328 cDNA, wherein SEQ ID NO:93 is a clone designated herein as "DNA66658-1584".

15 Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence PRO1329 cDNA, wherein SEQ ID NO:95 is a clone designated herein as "DNA66660-1585".

20 Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence PRO1340 cDNA, wherein SEQ ID NO:97 is a clone designated herein as "DNA66663-1598".

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

25 Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO1342 cDNA, wherein SEQ ID NO:99 is a clone designated herein as "DNA66674-1599".

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

30 Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO3579 cDNA, wherein SEQ ID NO:101 is a clone designated herein as "DNA68862-2546".

Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) of a native sequence PRO1472 cDNA, wherein SEQ ID NO:103 is a clone designated herein as "DNA68866-1644".

35 Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:103 shown in Figure 103.

Figure 105 shows a nucleotide sequence (SEQ ID NO:105) of a native sequence PRO1461 cDNA, wherein SEQ ID NO:105 is a clone designated herein as "DNA68871-1638".

Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

Figure 107 shows a nucleotide sequence (SEQ ID NO:107) of a native sequence PRO1568 cDNA, wherein SEQ ID NO:107 is a clone designated herein as "DNA68880-1676".

Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ ID NO:107 shown in Figure 107.

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) of a native sequence PRO1753 cDNA, wherein SEQ ID NO:109 is a clone designated herein as "DNA68883-1691".

Figure 110 shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:109 shown in Figure 109.

Figure 111 shows a nucleotide sequence (SEQ ID NO:111) of a native sequence PRO1570 cDNA, wherein SEQ ID NO:111 is a clone designated herein as "DNA68885-1678".

Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:111 shown in Figure 111.

Figure 113 shows a nucleotide sequence (SEQ ID NO:113) of a native sequence PRO1446 cDNA, wherein SEQ ID NO:113 is a clone designated herein as "DNA71277-1636".

Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figure 113.

Figure 115 shows a nucleotide sequence (SEQ ID NO:115) of a native sequence PRO1565 cDNA, wherein SEQ ID NO:115 is a clone designated herein as "DNA73727-1673".

Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:115 shown in Figure 115.

Figure 117 shows a nucleotide sequence (SEQ ID NO:117) of a native sequence PRO1572 cDNA, wherein SEQ ID NO:117 is a clone designated herein as "DNA73734-1680".

Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:117 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO:119) of a native sequence PRO1573 cDNA, wherein SEQ ID NO:119 is a clone designated herein as "DNA73735-1681".

Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:119 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:121) of a native sequence PRO1550 cDNA, wherein SEQ ID NO:121 is a clone designated herein as "DNA76393-1664".

Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:121 shown in Figure 121.

Figure 123 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO1693 cDNA, wherein SEQ ID NO:123 is a clone designated herein as "DNA77301-1708".

Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 123.

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) of a native sequence PRO1566 cDNA, wherein SEQ ID NO:125 is a clone designated herein as "DNA77568-1626".

Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

5 Figure 127 shows a nucleotide sequence (SEQ ID NO:127) of a native sequence PRO1774 cDNA, wherein SEQ ID NO:127 is a clone designated herein as "DNA77626-1705".

Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) of a native sequence PRO1928 cDNA, wherein SEQ ID NO:129 is a clone designated herein as "DNA81754-2532".

10 Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

Figure 131 shows a nucleotide sequence (SEQ ID NO:131) of a native sequence PRO1865 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "DNA81757-2512".

15 Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 131.

Figure 133 shows a nucleotide sequence (SEQ ID NO:133) of a native sequence PRO1925 cDNA, wherein SEQ ID NO:133 is a clone designated herein as "DNA82302-2529".

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ ID NO:133 shown in Figure 133.

20 Figure 135 shows a nucleotide sequence (SEQ ID NO:135) of a native sequence PRO1926 cDNA, wherein SEQ ID NO:135 is a clone designated herein as "DNA82340-2530".

Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

25 Figure 137 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO1801 cDNA, wherein SEQ ID NO:137 is a clone designated herein as "DNA83500-2506".

Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) of a native sequence PRO4405 cDNA, wherein SEQ ID NO:139 is a clone designated herein as "DNA84920-2614".

30 Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

Figure 141 shows a nucleotide sequence (SEQ ID NO:141) of a native sequence PRO3435 cDNA, wherein SEQ ID NO:141 is a clone designated herein as "DNA85066-2534".

35 Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:141 shown in Figure 141.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) of a native sequence PRO3543 cDNA, wherein SEQ ID NO:143 is a clone designated herein as "DNA86571-2551".

WO 01/16318

Figure 144 shows the amino acid sequence (SEQ ID NO:144) derived from the coding sequence of SEQ ID NO:143 shown in Figure 143.

Figure 145 shows a nucleotide sequence (SEQ ID NO:145) of a native sequence PRO3443 cDNA, wherein SEQ ID NO:145 is a clone designated herein as "DNA87991-2540".

Figure 146 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:145 shown in Figure 145.

Figure 147 shows a nucleotide sequence (SEQ ID NO:147) of a native sequence PRO3442 cDNA, wherein SEQ ID NO:147 is a clone designated herein as "DNA92238-2539".

Figure 148 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:147 shown in Figure 147.

Figure 149 shows a nucleotide sequence (SEQ ID NO:149) of a native sequence PRO5990 cDNA, wherein SEQ ID NO:149 is a clone designated herein as "DNA96042-2682".

Figure 150 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:149 shown in Figure 149.

Figure 151 shows a nucleotide sequence (SEQ ID NO:151) of a native sequence PRO4342 cDNA, wherein SEQ ID NO:151 is a clone designated herein as "DNA96787-2534".

Figure 152 shows the amino acid sequence (SEQ ID NO:152) derived from the coding sequence of SEQ ID NO:151 shown in Figure 151.

Figure 153 shows a nucleotide sequence (SEQ ID NO:153) of a native sequence PRO10096 cDNA, wherein SEQ ID NO:153 is a clone designated herein as "DNA125185-2806".

Figure 154 shows the amino acid sequence (SEQ ID NO:154) derived from the coding sequence of SEQ ID NO:153 shown in Figure 153.

Figure 155 shows a nucleotide sequence (SEQ ID NO:155) of a native sequence PRO10272 cDNA, wherein SEQ ID NO:155 is a clone designated herein as "DNA147531-2821".

Figure 156 shows the amino acid sequence (SEQ ID NO:156) derived from the coding sequence of SEQ ID NO:155 shown in Figure 155.

Figure 157 shows a nucleotide sequence (SEQ ID NO:157) of a native sequence PRO5801 cDNA, wherein SEQ ID NO:157 is a clone designated herein as "DNA115291-2681".

Figure 158 shows the amino acid sequence (SEQ ID NO:158) derived from the coding sequence of SEQ ID NO:157 shown in Figure 157.

Figure 159 shows a nucleotide sequence (SEQ ID NO:159) of a native sequence PRO20110 cDNA, wherein SEQ ID NO:159 is a clone designated herein as "DNA166819".

Figure 160 shows the amino acid sequence (SEQ ID NO:160) derived from the coding sequence of SEQ ID NO:159 shown in Figure 159.

Figure 161 shows a nucleotide sequence (SEQ ID NO:161) of a native sequence PRO20040 cDNA, wherein SEQ ID NO:161 is a clone designated herein as "DNA164625-2890".

Figure 162 shows the amino acid sequence (SEQ ID NO:162) derived from the coding sequence of SEQ ID NO:161 shown in Figure 161.

Figure 163 shows a nucleotide sequence (SEQ ID NO:163) of a native sequence PRO20233 cDNA, wherein SEQ ID NO:163 is a clone designated herein as "DNA165608".

Figure 164 shows the amino acid sequence (SEQ ID NO:164) derived from the coding sequence of SEQ ID NO:163 shown in Figure 163.

5 Figure 165 shows a nucleotide sequence (SEQ ID NO:165) of a native sequence PRO19670 cDNA, wherein SEQ ID NO:165 is a clone designated herein as "DNA131639-2874".

Figure 166 shows the amino acid sequence (SEQ ID NO:166) derived from the coding sequence of SEQ ID NO:165 shown in Figure 165.

Figure 167 shows a nucleotide sequence (SEQ ID NO:167) of a native sequence PRO1890 cDNA, wherein SEQ ID NO:167 is a clone designated herein as "DNA79230-2525".

10 Figure 168 shows the amino acid sequence (SEQ ID NO:168) derived from the coding sequence of SEQ ID NO:167 shown in Figure 167.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

15 The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, 20 administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptides disclosed herein.

25 A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence 30 polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino 35

acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid

sequence identity, alternatively at least about 91 % amino acid sequence identity, alternatively at least about 92 % amino acid sequence identity, alternatively at least about 93 % amino acid sequence identity, alternatively at least about 94 % amino acid sequence identity, alternatively at least about 95 % amino acid sequence identity, alternatively at least about 96 % amino acid sequence identity, alternatively at least about 97 % amino acid sequence identity, alternatively at least about 98 % amino acid sequence identity and alternatively at least about 99 % amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 30 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 60 amino acids in length, alternatively at least about 70 amino acids in length, alternatively at least about 80 amino acids in length, alternatively at least about 90 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 150 amino acids in length, alternatively at least about 200 amino acids in length, alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid 5 sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid 10 sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X", "Y" and "Z" each represent different hypothetical amino acid residues.

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % amino acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer 15 program (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring 20 matrix = BLOSUM62. When WU-BLAST-2 is employed, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (i.e., the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total 25 number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an the amino acid sequence A which has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., *Nucleic Acids Res.* 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the 30 National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino 35 acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino 5 acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid 10 sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% 15 nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic 20 acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence. 25

30 Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 210 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 35 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, 5 using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. 10 Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

15 In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

20
$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence 25 D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA", wherein "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule 30 against which the "PRO-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides.

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % nucleic acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 35 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and

scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i.e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which 5 may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-10 encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., *Nucleic Acids Res.* 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those 15 search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can 20 alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

25 where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

30 In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

35 "Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous

solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

5 An "isolated" PRO polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. 10 Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

15 The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

20 Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, 25 "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

30 The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody compositions with polyepitopic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

35 "Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when

complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

5 "Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash 10 consisting of 0.1 x SSC containing EDTA at 55°C.

15

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution 20 comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

25 The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino 30 acid residues).

35 As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any

WO 01/16318

immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-

forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains

on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993).

5 An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or 10 nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

15 An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

20 The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

25 By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

30 A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

35 A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

Table 1

40

45

50

55

Table 1 (cont?)

```

/*
 */
#include <stdio.h>
#include <ctype.h>

5      #define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define J MPS      1024     /* max jmps in an path */
#define MX       4      /* save if there's at least MX-1 bases since last jmp */

10     #define DMAT      3      /* value of matching bases */
#define DMIS      0      /* penalty for mismatched bases */
#define DINS0     8      /* penalty for a gap */
#define DINS1      1      /* penalty per base */
15     #define PINS0     8      /* penalty for a gap */
#define PINS1      4      /* penalty per residue */

20     struct jmp {
        short      n[MAXJMP]; /* size of jmp (neg for delay) */
        unsigned short x[MAXJMP]; /* base no. of jmp in seq x */
        /* limits seq to 2^16 -1 */
    };

25     struct diag {
        int      score; /* score at last jmp */
        long     offset; /* offset of prev block */
        short     ijmp; /* current jmp index */
        struct jmp  jp; /* list of jmps */
    };

30     struct path {
        int      spc; /* number of leading spaces */
        short     nJ MPS; /* size of jmp (gap) */
        int      x[J MPS]; /* loc of jmp (last elem before gap) */
    };

35     char      *ofile; /* output file name */
char      *namex[2]; /* seq names: getseqs() */
char      *prog; /* prog name for err msgs */
char      *seqx[2]; /* seqs: getseqs() */
40     int      dmax; /* best diag: nw() */
int      dmax0; /* final diag */
int      dna; /* set if dna: main() */
int      endgaps; /* set if penalizing end gaps */
int      gapx, gapy; /* total gaps in seqs */
45     int      len0, len1; /* seq lens */
int      ngapx, ngapy; /* total size of gaps */
int      smax; /* max score: nw() */
int      *xbm; /* bitmap for matching */
long     offset; /* current offset in jmp file */
50     struct diag  *dx; /* holds diagonals */
struct path   pp[2]; /* holds path for seqs */

55     char      *calloc(), *malloc(), *index(), *strcpy();
char      *getseq(), *g_calloc();

```

Table 1 (cont?)

```

/* Needleman-Wunsch alignment program
 *
 * usage: progs file1 file2
 *   where file1 and file2 are two dna or two protein sequences.
 *   The sequences can be in upper- or lower-case and may contain ambiguity
 *   Any lines beginning with ';' or '<' are ignored
 *   Max file length is 65535 (limited by unsigned short x in the jmp struct)
 *   A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
 *   Output is in the file "align.out"
 *
 * The program may create a tmp file in /tmp to hold info about traceback.
 * Original version developed under BSD 4.3 on a vax 8650
 */
#include "nw.h"
#include "day.h"

static _dbval[26] = {
  1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
  1, 2 |(1 < < ('D'-'A'))|(1 < < ('N'-'A')), 4, 8, 16, 32, 64,
  128, 256, 0xFFFFFFFF, 1 < < 10, 1 < < 11, 1 < < 12, 1 < < 13, 1 < < 14,
  1 < < 15, 1 < < 16, 1 < < 17, 1 < < 18, 1 < < 19, 1 < < 20, 1 < < 21, 1 < < 22,
  1 < < 23, 1 < < 24, 1 < < 25|(1 < < ('E'-'A'))|(1 < < ('Q'-'A'))
};

main(ac, av)
{
    int ac;
    char *av[ ];
    prog = av[0];
    if (ac != 3) {
        fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
        fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
    }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
    xbm = (dna)? _dbval : _pbval;

    endgaps = 0; /* 1 to penalize endgaps */
    ofile = "align.out"; /* output file */

    nw(); /* fill in the matrix, get the possible jmps */
    readjmps(); /* get the actual jmps */
    print(); /* print stats, alignment */

    cleanup(0); /* unlink any tmp files */
}

```

Table 1 (cont')

```

/* do the alignment, return best score: main()
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
 * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
5      nw()
{
10      char      *px, *py;          /* seqs and ptrs */
      int       *ndely, *dely;    /* keep track of dely */
      int       ndlx, delx;      /* keep track of delx */
      int       *tmp;           /* for swapping row0, row1 */
      int       mis;            /* score for each type */
      int       ins0, ins1;      /* insertion penalties */
15      register  id;            /* diagonal index */
      register  ij;            /* jmp index */
      register  *col0, *col1;    /* score for curr, last row */
      register  xx, yy;         /* index into seqs */
20      dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));
      ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
      dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
25      col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
      col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
      ins0 = (dna)? DINS0 : PINS0;
      ins1 = (dna)? DINS1 : PINS1;
30      smax = -10000;
      if (endgaps) {
          for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
              col0[yy] = dely[yy] = col0[yy-1] - ins1;
              ndely[yy] = yy;
35          }
          col0[0] = 0;      /* Waterman Bull Math Biol 84 */
      }
      else
          for (yy = 1; yy <= len1; yy++)
              dely[yy] = -ins0;
40      /* fill in match matrix
      */
45      for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
          /* initialize first entry in col
          */
          if (endgaps) {
              if (xx == 1)
                  col1[0] = delx = -(ins0+ins1);
50          else
              col1[0] = delx = col0[0] - ins1;
              ndlx = xx;
          }
          else {
55              col1[0] = 0;
              delx = -ins0;
              ndlx = 0;
          }
      }
60
      nw

```

Table 1 (cont')

...nw

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongong del
     * ignore MAXGAP if weighting endgaps
     */
    10   if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
     * favor new del over ongong del
     */
    25   if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
     * mis over any del and delx over dely
     */
    30
    35
    40
    45
    50
}

```

55

60

...nw

Table 1 (cont')

```

id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
    col1[yy] = mis;
5    else if (delx >= dely[yy]) {
        col1[yy] = delx;
        ij = dx[id].ijmp;
        if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
10   && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
            dx[id].ijmp++;
            if (++ij >= MAXJMP) {
                writejmps(id);
                ij = dx[id].ijmp = 0;
                dx[id].offset = offset;
                offset += sizeof(struct jmp) + sizeof(offset);
15
            }
        }
        dx[id].jp.n[ij] = ndelx;
        dx[id].jp.x[ij] = xx;
        dx[id].score = delx;
20
    }
    else {
        col1[yy] = dely[yy];
        ij = dx[id].ijmp;
25   if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
            && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                dx[id].ijmp++;
                if (++ij >= MAXJMP) {
                    writejmps(id);
                    ij = dx[id].ijmp = 0;
                    dx[id].offset = offset;
                    offset += sizeof(struct jmp) + sizeof(offset);
30
                }
            }
        dx[id].jp.n[ij] = -ndely[yy];
        dx[id].jp.x[ij] = xx;
        dx[id].score = dely[yy];
35
    }
    if (xx == len0 && yy < len1) {
        /* last col
        */
        if (endgaps)
            col1[yy] -= ins0+ins1*(len1-yy);
        if (col1[yy] > smax) {
40         smax = col1[yy];
            dmax = id;
        }
    }
45
}
50
if (endgaps && xx < len0)
    col1[yy-1] -= ins0+ins1*(len0-xx);
if (col1[yy-1] > smax) {
    smax = col1[yy-1];
    dmax = id;
55
}
tmp = col0; col0 = col1; col1 = tmp;
}
60
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
(void) free((char *)col1);
}

```

Table 1 (cont?)

```

/*
 *
 * print() -- only routine visible outside this module
 *
5  * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[ ]; print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
 * nums() -- put out a number line: dumpblock()
10 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() -- put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

15 #include "nw.h"

#define SPC      3
#define P_LINE   256      /* maximum output line */
#define P_SPC    3      /* space between name or num and seq */

20 extern _day[26][26];
int    olen;           /* set output line length */
FILE   *fx;            /* output file */

25 print()           print
{
    int    lx, ly, firstgap, lastgap; /* overlap */

30    if ((fx = fopen(ofile, "w")) == 0) {
        fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "< first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "< second sequence: %s (length = %d)\n", namex[1], len1);
    olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
40        pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
45        pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
50        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
55        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}

60

```

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
static
5  getmat(lx, ly, firstgap, lastgap)           getmat
      int      lx, ly;                      /* "core" (minus endgaps) */
      int      firstgap, lastgap;          /* leading/trailing overlap */
{
10    int          nm, i0, i1, siz0, siz1;
    char        outx[32];
    double      pct;
    register    n0, n1;
    register char *p0, *p1;

15    /* get total matches, score
     */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
20    n0 = pp[1].spc + 1;
    n1 = pp[0].spc + 1;

    nm = 0;
    while ( *p0 && *p1 ) {
25      if (siz0) {
          p1++;
          n1++;
          siz0--;
      }
30      else if (siz1) {
          p0++;
          n0++;
          siz1--;
      }
35      else {
          if (xbm[*p0-'A']&xbm[*p1-'A'])
              nm++;
          if (n0++ == pp[0].x[i0])
              siz0 = pp[0].n[i0++];
          if (n1++ == pp[1].x[i1])
              siz1 = pp[1].n[i1++];
          p0++;
          p1++;
      }
45    }

    /* pct homology:
     * if penalizing endgaps, base is the shorter seq
     * else, knock off overhangs and take shorter core
     */
50    if (endgaps)
        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
55    pct = 100.*(double)nm/(double)lx;
    fprintf(fx, "\n");
    fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
            nm, (nm == 1)? ":" : "es", lx, pct);

```

60

Table 1 (cont')

```

5   fprintf(fx, "<gaps in first sequence: %d", gapx);           ...getmat
  if (gapx) {
    (void) sprintf(outx, " (%d %s%s)", ngapx, (dna)? "base":"residue", (ngapx == 1)? ":"s");
    fprintf(fx,"%s", outx);

10  fprintf(fx, ", gaps in second sequence: %d", gapy);
  if (gapy) {
    (void) sprintf(outx, " (%d %s%s)", ngapy, (dna)? "base":"residue", (ngapy == 1)? ":"s");
    fprintf(fx,"%s", outx);
  }
  if (dna)
15   fprintf(fx,
    "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
    smax, DMAT, DMIS, DINS0, DINS1);
  else
20   fprintf(fx,
    "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
    smax, PINS0, PINS1);
  if (endgaps)
25   fprintf(fx,
    "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
    firstgap, (dna)? "base" : "residue", (firstgap == 1)? ":"s",
    lastgap, (dna)? "base" : "residue", (lastgap == 1)? ":"s");
  else
30   fprintf(fx, "<endgaps not penalized\n");
}

35  static nm;          /* matches in core -- for checking */
  static lmax;         /* lengths of stripped file names */
  static ij[2];        /* jmp index for a path */
  static nc[2];        /* number at start of current line */
  static ni[2];        /* current elem number -- for gapping */
  static siz[2];
  static char *ps[2];  /* ptr to current element */
  static char *po[2];  /* ptr to next output char slot */
40  static char out[2][P_LINE]; /* output line */
  static char star[P_LINE]; /* set by stars() */

  /*
   * print alignment of described in struct path pp [ ]
   */
45  static pr_align()
  {
    int nn;           /* char count */
    int more;
    register i;
50
    for (i = 0, lmax = 0; i < 2; i++) {
      nn = stripname(name[i]);
      if (nn > lmax)
        lmax = nn;

      nc[i] = 1;
      ni[i] = 1;
      siz[i] = ij[i] = 0;
      ps[i] = seqx[i];
      po[i] = out[i];
    }
  }
55
60

```

Table 1 (cont')

```

for (nn = nm = 0, more = 1; more; ) {
    for (i = more = 0; i < 2; i++) {
        /*
         * do we have more of this sequence?
         */
        if (!*ps[i])
            continue;

5           more++;

10          if (pp[i].spc) { /* leading space */
                *po[i]++ = ' ';
                pp[i].spc--;
            }
15          else if (siz[i]) { /* in a gap */
                *po[i]++ = '-';
                siz[i]--;
            }
20          else { /* we're putting a seq element
                */
                *po[i] = *ps[i];
                if (islower(*ps[i]))
                    *ps[i] = toupper(*ps[i]);
                po[i]++;
                ps[i]++;
            }

25          /*
           * are we at next gap for this seq?
           */
30          if (ni[i] == pp[i].x[ij[i]]) {
                /*
                 * we need to merge all gaps
                 * at this location
                 */
35                siz[i] = pp[i].n[ij[i]++];
                while (ni[i] == pp[i].x[ij[i]])
                    siz[i] += pp[i].n[ij[i]++];
            }
40          ni[i]++;
        }
        if (++nn == olen || !more && nn) {
            dumpblock();
            for (i = 0; i < 2; i++)
                po[i] = out[i];
            nn = 0;
        }
50    }

55    /*
     * dump a block of lines, including numbers, stars: pr_align()
     */
56    static
57    dumpblock()
58    {
59        register i;
60        for (i = 0; i < 2; i++)
            *po[i]-- = '\0';

```

...pr_align

dumpblock

Table 1 (cont')

```

...dumpblock

5   (void) putc('\n', fx);
    for (i = 0; i < 2; i++) {
        if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
            if (i == 0)
                nums(i);
            if (i == 0 && *out[1])
                stars();
10           putline(i);
            if (i == 0 && *out[1])
                fprintf(fx, star);
            if (i == 1)
                nums(i);
15           }
        }
    }

20  /*
     * put out a number line: dumpblock()
     */
static
25  nums(ix)
    int      ix;      /* index in out[] holding seq line */
    {
        char      nline[P_LINE];
        register  i, j;
        register char  *pn, *px, *py;

30  for (pn = nline, i = 0; i < lmax + P_SPC; i++, pn++)
        *pn = ' ';
    for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
        if (*py == ' ' || *py == '-')
            *pn = ' ';
35  else {
            if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                j = (i < 0)? -i : i;
                for (px = pn; j /= 10, px--)
                    *px = j%10 + '0';
                if (i < 0)
                    *px = '-';
            }
            else
                *pn = ' ';
40  }
        i++;
    }
    *pn = '\0';
    nc[ix] = i;
45  for (pn = nline; *pn; pn++)
        (void) putc(*pn, fx);
    (void) putc('\n', fx);
    }

50  /*
     * put out a line (name, [num], seq, {num}): dumpblock()
     */
static
55  putline(ix)
    int      ix;
    {

```

Table 1 (cont')

...putline

```

5      int          i;
register char    *px;
for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
    (void) putc(*px, fx);
for (; i < lmax+P_SPC; i++)
    (void) putc(' ', fx);

10     /* these count from 1:
* ni[] is current element (from 1)
* nc[] is number at start of current line
*/
15     for (px = out[ix]; *px; px++)
    (void) putc(*px&0x7F, fx);
    (void) putc('\n', fx);
}

20     /*
* put a line of stars (seqs always in out[0], out[1]): dumpblock()
*/
25     static stars()
{
30     int          i;
register char    *p0, *p1, cx, *px;
if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
    !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
    return;
px = star;
for (i = lmax+P_SPC; i; i--)
    *px++ = ' ';
35     for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
        if (isalpha(*p0) && isalpha(*p1)) {
40         if (xbm[*p0-'A']&xbm[*p1-'A']) {
            cx = '*';
            nm++;
        }
        else if (!dma && _day[*p0-'A'][*p1-'A'] > 0)
            cx = '.';
        else
            cx = ' ';
    }
    else
        cx = ' ';
50     *px++ = cx;
}
*px++ = '\n';
*px = '\0';
55     }

60

```

Table 1 (cont')

```

/*
 * strip path or prefix from pn. return len: pr_align()
 */
static
5    stripname(pn)
        char      *pn;      /* file name (may be path) */
{
    register char      *px, *py;

10   py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;
15   if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}

20

25

30

35

40

45

50

55

60

```

Table 1 (cont')

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
 5   * readjmps() -- get the good jmps, from tmp file if necessary
 * writejmps() -- write a filled array of jmps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>
10
char  *jname = "/tmp/homgXXXXXX";           /* tmp file for jmps */
FILE  *fj;
15
int   cleanup();                         /* cleanup tmp file */
long  lseek();
1
/*
 * remove any tmp file if we blow
 */
20
cleanup(i)
    int   i;
{
    if (fj)
        (void) unlink(jname);
25
    exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
30
char  *
getseq(file, len)
35
    char  *file;   /* file name */
    int   *len;    /* seq len */
{
    char  line[1024], *pseq;
    register char *px, *py;
40
    int   natgc, tlen;
    FILE *fp;
45
    if ((fp = fopen(file, "r")) == 0) {
        fprintf(stderr, "%s: can't read %s\n", prog, file);
        exit(1);
    }
    tlen = natgc = 0;
    while (fgets(line, 1024, fp)) {
        if (*line == ';' || *line == '<' || *line == '>')
50
            continue;
        for (px = line; *px != '\n'; px++)
            if (isupper(*px) || islower(*px))
                tlen++;
    }
    if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
55
        fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
    pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
60

```

cleanup

getseq

Table 1 (cont')

```

...getseq

5      py = pseq + 4;
*len = tlen;
rewind(fp);

10     while (fgets(line, 1024, fp)) {
        if (*line == ';' || *line == '<' || *line == '>')
            continue;
        for (px = line; *px != '\n'; px++) {
            if (isupper(*px))
                *py++ = *px;
            else if (islower(*px))
                *py++ = toupper(*px);
            if (index("ATGCU", *(py-1)))
                natgc++;
        }
        *py++ = '\0';
*py = '\0';
(void) fclose(fp);
dna = natgc > (tlen/3);
return(pseq+4);
}

25     char * g_malloc
g_malloc(msg, nx, sz)
    char *msg;          /* program, calling routine */
    int nx, sz;         /* number and size of elements */
{
    char *px, *calloc();

30     if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
        if (*msg) {
            fprintf(stderr, "%s: g_malloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
}

40     /*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
 */
readjmps()
45     {
        int fd = -1;
        int siz, i0, i1;
        register i, j, xx;

50     if (fj) {
            (void) fclose(fj);
            if ((fd = open(jname, O_RDONLY, 0)) < 0) {
                fprintf(stderr, "%s: can't open() %s\n", prog, jname);
                cleanup(1);
            }
        }
        for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
            while (1) {
                for (j = dx[dmax].jmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                    ;
            }
        }
    }

55
60

```

Table 1 (cont')

...readjmps

```

5      if (j < 0 && dx[dmax].offset && fj) {
          (void) lseek(fd, dx[dmax].offset, 0);
          (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
          (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
          dx[dmax].ijmp = MAXJMP-1;
      }
      else
          break;
10     }
      if (i >= JMPS) {
          fprintf(stderr, "%s: too many gaps in alignment\n", prog);
          cleanup(1);
      }
15     if (j >= 0) {
          siz = dx[dmax].jp.n[j];
          xx = dx[dmax].jp.x[j];
          dmax += siz;
          if (siz < 0) { /* gap in second seq */
              pp[1].n[i1] = -siz;
              xx += siz;
              /* id = xx - yy + len1 - 1
               */
              pp[1].x[i1] = xx - dmax + len1 - 1;
              gapy++;
              ngapy -= siz;
          }
          /* ignore MAXGAP when doing endgaps */
          siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
          i1++;
20     }
25     /* ignore MAXGAP when doing endgaps */
          siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
          i0++;
30     }
35     /* ignore MAXGAP when doing endgaps */
          siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
          i0++;
      }
40     }
45     /* reverse the order of jmps
     */
      for (j = 0, i0--; j < i0; j++, i0--) {
          i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
          i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
50     }
      for (j = 0, i1--; j < i1; j++, i1--) {
          i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
          i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
      }
55     if (fd >= 0)
          (void) close(fd);
      if (fj) {
          (void) unlink(jname);
          fj = 0;
          offset = 0;
60     }
  
```

Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
5   writejmps(ix)
      int      ix;
{
      char    *mktemp();

10  if (!fj) {
      if (mktemp(jname) < 0) {
          fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
          cleanup(1);
      }
15  if ((fj = fopen(jname, "w")) == 0) {
          fprintf(stderr, "%s: can't write %s\n", prog, jname);
          exit(1);
      }
20  (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
  (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}

25

30

35

40

45

50

55

60

```

Table 2

PRO	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXYYYYYYYYY	(Length = 12 amino acids)
5	% amino acid sequence identity =	(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =
10	5 divided by 15 = 33.3%	

Table 3

PRO	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXXXXYYYYYYZZYZ	(Length = 15 amino acids)

5 % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

10 5 divided by 10 = 50%

Table 4

PRO-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNNLLLLLLLL	(Length = 16 nucleotides)

5 % nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

10 6 divided by 14 = 42.9%

Table 5

PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

5 % nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

10 4 divided by 12 = 33.3%

II. Compositions and Methods of the InventionA. Full-Length PRO Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

B. PRO Polypeptide Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired 5 termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed 10 herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial 15 changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

<u>Original Residue</u>	<u>Exemplary Substitutions</u>	<u>Preferred Substitutions</u>
5 Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; lys; arg	gln
Asp (D)	glu	glu
Cys (C)	ser	ser
10 Gln (Q)	asn	asn
Glu (E)	asp	asp
Gly (G)	pro; ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
15 Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
20 Phe (F)	leu; val; ile; ala; tyr	leu
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
25 Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished

30 by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- 35 (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

40 Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London Ser A,

317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, *Science*, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, *The Proteins*, (W.H. Freeman & Co., N.Y.); Chothia, *J. Mol. Biol.*, 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

10

C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate.

Other modifications include deamidation of glutamyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the

desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

5 Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety 10 of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

15 The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples 20 include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8E9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the 25 Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an α -tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

30 In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred 35 embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart 5 et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length 10 PRO.

1. Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently 15 obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA 20 or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences 25 selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known 30 sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic 35 libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting 5 transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending on the host cell 10 used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells 15 without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, 20 electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are 25 publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescens*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), 30 *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous 35 to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7*

ilvG kan'; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

5 In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, *Nature*, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., *Bio/Technology*, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., *J. Bacteriol.*, 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickeramii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilicola* (ATCC 36,906; Van den Berg et al., *Bio/Technology*, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., *J. Basic Microbiol.*, 28:265-278 [1988]); *Candida*; *Trichoderma reesiae* (EP 244,234); *Neurospora crassa* (Case et al., *Proc. Natl. Acad. Sci. USA*, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, 15 e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., *Biochem. Biophys. Res. Commun.*, 112:284-289 [1983]; Tilburn et al., *Gene*, 26:205-221 [1983]; Yelton et al., *Proc. Natl. Acad. Sci. USA*, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, *EMBO J.*, 4:475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, 20 *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, *The Biochemistry of Methylotrophs*, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila S2* and *Spodoptera Sf9*, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. 25 More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., *J. Gen Virol.*, 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, *Biol. Reprod.*, 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 30 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector 35 may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally

WO 01/16318

include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., *Proc. Natl. Acad. Sci. USA*, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., *Nature*, 282:39 (1979); Kingsman et al., *Gene*, 7:141 (1979); Tschemper et al., *Gene*, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, *Genetics*, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., *Nature*, 275:615 (1978); Goeddel et al., *Nature*, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, *Nucleic Acids Res.*, 8:4057 (1980); EP 36,776], and hybrid

promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytchrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

5. Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

E. Uses for PRO

Nucleotide sequences (or their complement) encoding PRO have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO nucleic acid will also be useful for the preparation of PRO polypeptides by the recombinant techniques described herein.

The full-length native sequence PRO gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length PRO cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of PRO or PRO from other species) which have a desired sequence identity to the native PRO sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native 5 nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence PRO. By way of example, a screening method will comprise isolating the coding region of the PRO gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ^{32}P or ^{35}S , or enzymatic labels such as alkaline phosphatase coupled to the 10 probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the PRO gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

Any EST sequences disclosed in the present application may similarly be employed as probes, using 15 the methods disclosed herein.

Other useful fragments of the PRO nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO mRNA (sense) or PRO DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of PRO DNA. Such a fragment generally comprises at least about 14 20 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (*Cancer Res.* 48:2659, 1988) and van der Krol et al. (*BioTechniques* 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including 25 enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. The antisense oligonucleotides thus may be used to block expression of PRO proteins. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of 30 resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases 35 affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO_4 -mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

Antisense or sense RNA or DNA molecules are generally at least about 5 bases in length, about 10 bases in length, about 15 bases in length, about 20 bases in length, about 25 bases in length, about 30 bases in length, about 35 bases in length, about 40 bases in length, about 45 bases in length, about 50 bases in length, about 55 bases in length, about 60 bases in length, about 65 bases in length, about 70 bases in length, about 75 bases in length, about 80 bases in length, about 85 bases in length, about 90 bases in length, about 95 bases in length, about 100 bases in length, or more.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO coding sequences.

Nucleotide sequences encoding a PRO can also be used to construct hybridization probes for mapping the gene which encodes that PRO and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for PRO encode a protein which binds to another protein (example, where the PRO is a receptor), the PRO can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor PRO can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native PRO or a receptor for PRO. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small

molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

Nucleic acids which encode PRO or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding PRO. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for PRO transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding PRO introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding PRO. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of PRO can be used to construct a PRO "knock out" animal which has a defective or altered gene encoding PRO as a result of homologous recombination between the endogenous gene encoding PRO and altered genomic DNA encoding PRO introduced into an embryonic stem cell of the animal. For example, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques. A portion of the genomic DNA encoding PRO can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of

the PRO polypeptide.

Nucleic acid encoding the PRO polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik *et al.*, Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau *et al.*, Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem. 262, 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson *et al.*, Science 256, 808-813 (1992).

The PRO polypeptides described herein may also be employed as molecular weight markers for protein electrophoresis purposes and the isolated nucleic acid sequences may be used for recombinantly expressing those markers.

The nucleic acid molecules encoding the PRO polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each PRO nucleic acid molecule of the present invention can be used as a chromosome marker.

The PRO polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. PRO nucleic acid molecules will find use for generating probes for PCR, Northern

analysis, Southern analysis and Western analysis.

The PRO polypeptides described herein may also be employed as therapeutic agents. The PRO polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO product hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, PLURONICS™ or PEG.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The use of interspecies scaling in toxicokinetics" In *Toxicokinetics and New Drug Development*, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When *in vivo* administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1 μ g/kg/day to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO

WO 01/16318

polypeptide, microencapsulation of the PRO polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon-
proteins (rhIFN-), interleukin-2, and MN rgp120. Johnson et al., Nat. Med., 2:795-799 (1996); Yasuda, Biomed. Ther., 27:1221-1223 (1993); Hora et al., Bio/Technology, 8:755-758 (1990); Cleland, "Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in Vaccine Design: The Subunit and Adjuvant Approach, Powell and Newman, eds, (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/07399; and U.S. Pat. No. 5,654,010.

5 The sustained-release formulations of these proteins were developed using poly-lactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41.

10 This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for 15 antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

20 The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a PRO 25 polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

25 In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent 30 attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized 35 component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody 40 specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKERTM) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the PRO polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991).

Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and 5 incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is 10 resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro- sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor 15 would be incubated with labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and 20 monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the 25 PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using 25 antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide 30 sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby 35 preventing transcription and the production of the PRO polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO

polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

5 Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, *Current Biology*, 4:469-471 (1994), and PCT publication 10 No. WO 97/33551 (published September 18, 1997).

15 Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

20 Diagnostic and therapeutic uses of the herein disclosed molecules may also be based upon the positive functional assay hits disclosed and described below.

F. Anti-PRO Antibodies

25 The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies

30 The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). 35 The immunization protocol may be selected by one skilled in the art without undue experimentation.

2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

5 The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103].
10 Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine
15 guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

25 The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

30 After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

35 The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., *supra*] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones

WO 01/16318

et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks et al., Bio/Technology 10, 779-783 (1992); Lonberg et al., Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild et al., Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

The antibodies may also be affinity matured using known selection and/or mutagenesis methods as described above. Preferred affinity matured antibodies have an affinity which is five times, more preferably 10 times, even more preferably 20 or 30 times greater than the starting antibody (generally murine, humanized or human) from which the matured antibody is prepared.

30

4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain

pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')₂ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

WO 01/16318

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. 5 This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with 10 the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, J. Immunol. 152:5368 (1994). Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, J. Immunol. 147:60 (1991).

15 Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein. Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (Fc γ R), such as Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize 20 cytotoxic agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

25 5. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* 30 using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptoputyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

35 6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be

introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* 5 Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-Cancer Drug Design, 3: 219-230 (1989).

7. Immunoconjugates

10 The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active 15 fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the trichothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ²¹²Bi, ¹³¹I, ¹³¹In, ⁹⁰Y, and ¹⁸⁶Re.

20 Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridylthiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-disfluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent 25 for conjugation of radionucleotide to the antibody. See WO94/11026.

30 In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

8. Immunoliposomes

35 The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos.

WO 01/16318

4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. 5 Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, J. National Cancer Inst., 81(19): 1484 (1989).

10 9. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

15 If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target 20 protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, *e.g.*, Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993). The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic 25 agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions.

30 Such techniques are disclosed in Remington's Pharmaceutical Sciences, supra.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

35 Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), poly(lactides) (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl

acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulphydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

10

G. Uses for anti-PRO Antibodies

The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, e.g., detecting its expression (and in some cases, differential expression) in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144:945 (1962); David et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol. Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem., 30:407 (1982).

25

Anti-PRO antibodies also are useful for the affinity purification of PRO from recombinant cell culture or natural sources. In this process, the antibodies against PRO are immobilized on a suitable support, such a Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the PRO to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO from the antibody.

30

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

35

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

5

EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST-2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

10 Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST or BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

15 Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5 kbp. In order to screen 20 several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., *Current Protocols in Molecular Biology*, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

25 The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with 30 oligo dT containing a NotI site, linked with blunt to Sall hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRK5B or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

35

EXAMPLE 2: Isolation of cDNA clones by Amylase Screening1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System).

5 In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linker cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

2. Preparation of random primed cDNA library

10 A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linker with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI 15 cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

20

3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was 25 added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, e.g. CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the 30 plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL⁺, SUC⁺, GAL⁺. Preferably, yeast mutants can be 35 employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in sec71, sec72, sec62, with truncated sec71 being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins

WO 01/16318

implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz et al., Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2×10^6 cells/ml (approx. OD₆₀₀=0.1) into fresh YEPD broth (500 ml) and regrown to 1×10^7 cells/ml (approx. OD₆₀₀=0.4-0.5).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li₂OOCCH₃), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100 µl) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 µg, vol. < 10 µl) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 µl, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li₂OOCCH₃, pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 µl, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 µl) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely et al., Anal. Biochem., 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 μ l) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 μ l) was used as a template for the PCR reaction in a 25 μ l volume containing: 0.5 μ l Klentaq (Clontech, Palo Alto, CA); 4.0 μ l 10 mM dNTP's (Perkin Elmer-Cetus); 2.5 μ l Kentaq buffer (Clontech); 0.25 μ l forward oligo 1; 0.25 μ l reverse oligo 2; 12.5 μ l distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAAAACGACGGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:169)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:170)

10 PCR was then performed as follows:

a.		Denature	92°C, 5 minutes
b.	3 cycles of:	Denature	92°C, 30 seconds
		Anneal	59°C, 30 seconds
15		Extend	72°C, 60 seconds
c.	3 cycles of:	Denature	92°C, 30 seconds
		Anneal	57°C, 30 seconds
20		Extend	72°C, 60 seconds
d.	25 cycles of:	Denature	92°C, 30 seconds
		Anneal	55°C, 30 seconds
		Extend	72°C, 60 seconds
25	e.	Hold	4°C

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the 30 sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 μ l) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et al., supra. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing 35 after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as 40 clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine

codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven 5 sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

EXAMPLE 4: Isolation of cDNA Clones Encoding Human PRO Polypeptides

Using the techniques described in Examples 1 to 3 above, numerous full-length cDNA clones were 10 identified as encoding PRO polypeptides as disclosed herein. These cDNAs were then deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below.

Table 7

	<u>Material</u>	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
15	DNA26843-1389	203099	August 4, 1998
	DNA30867-1335	209807	April 28, 1998
	DNA34431-1177	209399	October 17, 1997
	DNA38268-1188	209421	October 28, 1997
20	DNA40621-1440	209922	June 2, 1998
	DNA40625-1189	209788	April 21, 1998
	DNA45409-2511	203579	January 12, 1999
	DNA45495-1550	203156	August 25, 1998
	DNA49820-1427	209932	June 2, 1998
25	DNA56406-1704	203478	November 17, 1998
	DNA56410-1414	209923	June 2, 1998
	DNA56436-1448	209902	May 27, 1998
	DNA56855-1447	203004	June 23, 1998
	DNA56860-1510	209952	June 9, 1998
30	DNA56862-1343	203174	September 1, 1998
	DNA56868-1478	203024	June 23, 1998
	DNA56869-1545	203161	August 25, 1998
	DNA57704-1452	209953	June 9, 1998
	DNA58723-1588	203133	August 18, 1998
35	DNA57827-1493	203045	July 1, 1998
	DNA58737-1473	203136	August 18, 1998
	DNA58846-1409	209957	June 9, 1998
	DNA58850-1495	209956	June 9, 1998
	DNA58855-1422	203018	June 23, 1998
40	DNA59211-1450	209960	June 9, 1998
	DNA59212-1627	203245	September 9, 1998
	DNA59213-1487	209959	June 9, 1998
	DNA59605-1418	203005	June 23, 1998
	DNA59609-1470	209963	June 9, 1998
45	DNA59610-1556	209990	June 16, 1998
	DNA59837-2545	203658	February 9, 1999
	DNA59844-2542	203650	February 9, 1999
	DNA59854-1459	209974	June 16, 1998

Table 7 (cont')

5	DNA60625-1507	209975	June 16, 1998
	DNA60629-1481	209979	June 16, 1998
	DNA61755-1554	203112	August 11, 1998
	DNA62812-1594	203248	September 9, 1998
	DNA62815-1576	203247	September 9, 1998
10	DNA64881-1602	203240	September 9, 1998
	DNA64886-1601	203241	September 9, 1998
	DNA64902-1667	203317	October 6, 1998
	DNA64950-1590	203224	September 15, 1998
	DNA65403-1565	203230	September 15, 1998
15	DNA66308-1537	203159	August 25, 1998
	DNA66519-1535	203236	September 15, 1998
	DNA66521-1583	203225	September 15, 1998
	DNA66658-1584	203229	September 15, 1998
	DNA66660-1585	203279	September 22, 1998
	DNA66663-1598	203268	September 22, 1998
	DNA66674-1599	203281	September 22, 1998
20	DNA68862-2546	203652	February 9, 1999
	DNA68866-1644	203283	September 22, 1998
	DNA68871-1638	203280	September 22, 1998
	DNA68880-1676	203319	October 6, 1998
	DNA68883-1691	203535	December 15, 1998
25	DNA68885-1678	203311	October 6, 1998
	DNA71277-1636	203285	September 22, 1998
	DNA73727-1673	203459	November 3, 1998
	DNA73734-1680	203363	October 20, 1998
	DNA73735-1681	203356	October 20, 1998
30	DNA76393-1664	203323	October 6, 1998
	DNA77301-1708	203407	October 27, 1998
	DNA77568-1626	203134	August 18, 1998
	DNA77626-1705	203536	December 15, 1998
	DNA81754-2532	203542	December 15, 1998
35	DNA81757-2512	203543	December 15, 1998
	DNA82302-2529	203534	December 15, 1998
	DNA82340-2530	203547	December 22, 1998
	DNA83500-2506	203391	October 29, 1998
	DNA84920-2614	203966	April 27, 1999
40	DNA85066-2534	203588	January 12, 1999
	DNA86571-2551	203660	February 9, 1999
	DNA87991-2540	203656	February 9, 1999
	DNA92238-2539	203602	January 20, 1999
	DNA96042-2682	PTA-382	July 20, 1999
45	DNA96787-2534	203589	January 12, 1999
	DNA125185-2806	PTA-1031	December 7, 1999
	DNA147531-2821	PTA-1185	January 11, 2000
	DNA115291-2681	PTA-202	June 8, 1999
	DNA164625-28890	PTA-1535	March 21, 2000
	DNA131639-2874	PTA-1784	April 25, 2000
50	DNA79230-2525	203549	December 22, 1998

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The

WO 01/16318

deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

5 The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license 10 to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

EXAMPLE 5: Use of PRO as a hybridization probe

15 The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe. DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

20 Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

25 DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

EXAMPLE 6: Expression of PRO in *E. coli*

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

30 The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., *Gene*, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode 35 for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

5 Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

10 After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

15 PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(laclq)). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5.36 g Difco 20 yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

25 *E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate 30 column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

35 The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The

WO 01/16318

refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

5 Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

10 15 Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 7: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

20 The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called pRK5-PRO.

25 In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-PRO DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

30 35 Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml ³⁵S-cysteine and 200 µCi/ml ³⁵S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in

serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrac et al., Proc. Natl. Acad. Sci., 75:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 μ g/ml bovine insulin and 0.1 μ g/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

10 In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO₄ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ³⁵S-methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium 15 is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

20 Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells 25 can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni²⁺-chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO 25 cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

30 Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early 35 promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

WO 01/16318

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect[®] (Qiagen), Doper[®] or Fugene[®] (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3×10^7 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μ m filtered PS20 with 5% 0.2 μ m diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3×10^5 cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2×10^6 cells/mL. On day 0, the cell number pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 mL/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 mL G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 mL Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 mL fractions into tubes containing 275 μ L of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 8: Expression of PRO in Yeast

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 9: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfected the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm

WO 01/16318

filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A₂₈₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching 5 A₂₈₀ baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₁₀-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known 10 chromatography techniques, including for instance, Protein A or protein G column chromatography.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 10: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

15 Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

20 Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice 25 by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

30 After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

35 The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively,

affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 11: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide 5 is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). 10 Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

15 Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

20 A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

25

EXAMPLE 12: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located 30 intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex 35 formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with

an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

5 Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted 10 with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

15 This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

EXAMPLE 13: Rational Drug Design

20 The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, *Bio/Technology*, 9: 19-21 (1991)).

25 In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. 30 In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, *Biochemistry*, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, *J. Biochem.*, 113:742-746 (1993).

35 It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic

antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

EXAMPLE 14: Pericyte c-Fos Induction (Assay 93)

This assay shows that certain polypeptides of the invention act to induce the expression of c-fos in pericyte cells and, therefore, are useful not only as diagnostic markers for particular types of pericyte-associated tumors but also for giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors. Induction of c-fos expression in pericytes is also indicative of the induction of angiogenesis and, as such, PRO polypeptides capable of inducing the expression of c-fos would be expected to be useful for the treatment of conditions where induced angiogenesis would be beneficial including, for example, wound healing, and the like. Specifically, on day 1, pericytes are received from VEC Technologies and all but 5 ml of media is removed from flask. On day 2, the pericytes are trypsinized, washed, spun and then plated onto 96 well plates. On day 7, the media is removed and the pericytes are treated with 100 μ l of PRO polypeptide test samples and controls (positive control = DME+5% serum +/- PDGF at 500 ng/ml; negative control = protein 32). Replicates are averaged and SD/CV are determined. Fold increase over Protein 32 (buffer control) value indicated by chemiluminescence units (RLU) luminometer reading versus frequency is plotted on a histogram. Two-fold above Protein 32 value is considered positive for the assay. ASY Matrix: Growth media = low glucose DMEM = 20% FBS + 1X pen strep + 1X fungizone. Assay Media = low glucose DMEM +5% FBS.

The following polypeptides tested positive in this assay: PRO1347 and PRO1340.

EXAMPLE 15: Ability of PRO Polypeptides to Stimulate the Release of Proteoglycans from Cartilage (Assay 97)

The ability of various PRO polypeptides to stimulate the release of proteoglycans from cartilage tissue was tested as follows.

The metacarpophalangeal joint of 4-6 month old pigs was aseptically dissected, and articular cartilage was removed by free hand slicing being careful to avoid the underlying bone. The cartilage was minced and cultured in bulk for 24 hours in a humidified atmosphere of 95% air, 5% CO₂ in serum free (SF) media (DME/F12 1:1) with 0.1% BSA and 100U/ml penicillin and 100 μ g/ml streptomycin. After washing three times, approximately 100 mg of articular cartilage was aliquoted into micronics tubes and incubated for an additional 24 hours in the above SF media. PRO polypeptides were then added at 1% either alone or in combination with 18 ng/ml interleukin-1 α , a known stimulator of proteoglycan release from cartilage tissue.

The supernatant was then harvested and assayed for the amount of proteoglycans using the 1,9-dimethyl-methylene blue (DMB) colorimetric assay (Farndale and Buttle, *Biochem. Biophys. Acta* 883:173-177 (1985)). A positive result in this assay indicates that the test polypeptide will find use, for example, in the treatment of sports-related joint problems, articular cartilage defects, osteoarthritis or rheumatoid arthritis.

When various PRO polypeptides were tested in the above assay, the polypeptides demonstrated a marked ability to stimulate release of proteoglycans from cartilage tissue both basally and after stimulation with interleukin-1 α and at 24 and 72 hours after treatment, thereby indicating that these PRO polypeptides are useful for stimulating proteoglycan release from cartilage tissue. As such, these PRO polypeptides are useful for the treatment of sports-related joint problems, articular cartilage defects, osteoarthritis or rheumatoid arthritis. The polypeptides testing positive in this assay are: PRO1565, PRO1693, PRO1801 and PRO10096.

10

EXAMPLE 16: Detection of Polypeptides That Affect Glucose or FFA Uptake in Skeletal Muscle (Assay 106)

This assay is designed to determine whether PRO polypeptides show the ability to affect glucose or FFA uptake by skeletal muscle cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of disorders where either the stimulation or inhibition of glucose uptake by skeletal muscle would be beneficial including, for example, diabetes or hyper- or hypo-insulinemia.

In a 96 well format, PRO polypeptides to be assayed are added to primary rat differentiated skeletal muscle, and allowed to incubate overnight. Then fresh media with the PRO polypeptide and +/- insulin are added to the wells. The sample media is then monitored to determine glucose and FFA uptake by the skeletal muscle cells. The insulin will stimulate glucose and FFA uptake by the skeletal muscle, and insulin in media without the PRO polypeptide is used as a positive control, and a limit for scoring. As the PRO polypeptide being tested may either stimulate or inhibit glucose and FFA uptake, results are scored as positive in the assay if greater than 1.5 times or less than 0.5 times the insulin control.

The following PRO polypeptides tested positive as either stimulators or inhibitors of glucose and/or FFA uptake in this assay: PRO4405.

25

EXAMPLE 17: Identification of PRO Polypeptides That Stimulate TNF- α Release In Human Blood (Assay 128)

This assay shows that certain PRO polypeptides of the present invention act to stimulate the release of TNF- α in human blood. PRO polypeptides testing positive in this assay are useful for, among other things, research purposes where stimulation of the release of TNF- α would be desired and for the therapeutic treatment of conditions wherein enhanced TNF- α release would be beneficial. Specifically, 200 μ l of human blood supplemented with 50mM Hepes buffer (pH 7.2) is aliquotted per well in a 96 well test plate. To each well is then added 300 μ l of either the test PRO polypeptide in 50 mM Hepes buffer (at various concentrations) or 50 mM Hepes buffer alone (negative control) and the plates are incubated at 37°C for 6 hours. The samples are then centrifuged and 50 μ l of plasma is collected from each well and tested for the presence of TNF- α by ELISA assay. A positive in the assay is a higher amount of TNF- α in the PRO polypeptide treated samples as compared to the negative control samples.

The following PRO polypeptides tested positive in this assay: PRO263, PRO295, PRO1282, PRO1063, PRO1356, PRO3543, and PRO5990.

EXAMPLE 18: Tumor Versus Normal Differential Tissue Expression Distribution

Oligonucleotide probes were constructed from some of the PRO polypeptide-encoding nucleotide sequences shown in the accompanying figures for use in quantitative PCR amplification reactions. The oligonucleotide probes were chosen so as to give an approximately 200-600 base pair amplified fragment from the 3' end of its associated template in a standard PCR reaction. The oligonucleotide probes were employed in standard quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in the various tumor and normal tissues tested. β -actin was used as a control to assure that equivalent amounts of nucleic acid was used in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. These assays provided the following results.

	<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
20	DNA26843-1389	normal lung rectum tumor	lung tumor normal rectum
25	DNA30867-1335	normal kidney	kidney tumor
30	DNA40621-1440	normal lung	lung tumor
35	DNA40625-1189	normal lung	lung tumor
40	DNA45409-2511	melanoma tumor	normal skin
45	DNA56406-1704	kidney tumor normal skin	normal kidney melanoma tumor
	DNA56410-1414	normal stomach	stomach tumor
	DNA56436-1448	normal skin	melanoma tumor
	DNA56855-1447	normal esophagus rectum tumor	esophageal tumor normal rectum
	DNA56860-1510	normal kidney rectum tumor	kidney tumor normal rectum
	DNA56862-1343	kidney tumor normal lung	normal kidney lung tumor

<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
DNA56868-1478	normal stomach normal lung	stomach tumor lung tumor
5 DNA56869-1545	normal esophagus normal skin	esophageal tumor melanoma tumor
DNA57704-1452	normal stomach rectum tumor	stomach tumor normal rectum
10 DNA58723-1588	normal stomach kidney tumor normal skin	stomach tumor normal kidney melanoma tumor
15 DNA57827-1493	normal stomach normal skin	stomach tumor melanoma tumor
DNA58737-1473	esophageal tumor normal stomach	normal esophagus stomach tumor
20 DNA58846-1409	lung tumor	normal lung
DNA58850-1495	esophageal tumor kidney tumor	normal esophagus normal kidney
25 DNA58855-1422	normal stomach rectum tumor	stomach tumor normal rectum
DNA59211-1450	normal kidney	kidney tumor
30 DNA59212-1627	normal skin	melanoma tumor
DNA59213-1487	normal stomach normal skin	stomach tumor melanoma tumor
35 DNA59605-1418	melanoma tumor	normal skin
DNA59609-1470	esophageal tumor	normal esophagus
40 DNA59610-1556	esophageal tumor lung tumor normal skin	normal esophagus normal lung melanoma tumor
DNA59837-2545	normal skin	melanoma tumor
45 DNA59844-2542	normal skin esophageal tumor	melanoma tumor normal esophagus
DNA59854-1459	normal esophagus stomach tumor normal lung	esophageal tumor normal stomach lung tumor
50 DNA60625-1507	normal lung	lung tumor
55 DNA60629-1481	normal esophagus normal rectum	esophageal tumor rectum tumor

<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
DNA61755-1554	normal stomach kidney tumor	stomach tumor normal kidney
5 DNA62812-1594	normal stomach normal lung normal rectum normal skin	stomach tumor lung tumor rectum tumor melanoma tumor
10 DNA62815-1576	esophageal tumor	normal esophagus
DNA64881-1602	normal stomach normal lung	stomach tumor lung tumor
15 DNA64902-1667	esophageal tumor kidney tumor	normal esophagus normal kidney
DNA65403-1565	normal esophagus	esophageal tumor
20 DNA66308-1537	normal lung	lung tumor
DNA66519-1535	kidney tumor	normal kidney
25 DNA66521-1583	normal esophagus normal stomach normal lung normal rectum normal skin	esophageal tumor stomach tumor lung tumor rectum tumor melanoma tumor
30 DNA66658-1584	normal lung melanoma tumor	lung tumor normal skin
DNA66660-1585	lung tumor	normal lung
35 DNA66674-1599	kidney tumor normal lung	normal kidney lung tumor
DNA68862-2546	melanoma tumor	normal skin
40 DNA68866-1644	normal stomach	stomach tumor
DNA68871-1638	lung tumor normal skin	normal lung melanoma tumor
45 DNA68880-1676	normal lung normal skin	lung tumor melanoma tumor
DNA68883-1691	esophageal tumor	normal esophagus
50 DNA68885-1678	lung tumor	normal lung
DNA71277-1636	normal stomach	stomach tumor
DNA73734-1680	normal lung	lung tumor

<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
DNA73735-1681	esophageal tumor normal kidney lung tumor normal skin	normal esophagus kidney tumor normal lung melanoma tumor
5 DNA76393-1664	esophageal tumor stomach tumor lung tumor rectum tumor	normal esophagus normal stomach normal lung normal rectum
10 DNA77568-1626	normal stomach lung tumor	stomach tumor normal lung
15 DNA77626-1705	normal rectum	rectum tumor
DNA81754-2532	normal skin	melanoma tumor
20 DNA81757-2512	esophageal tumor normal stomach melanoma tumor	normal esophagus stomach tumor normal skin
DNA82302-2529	normal stomach normal lung	stomach tumor lung tumor
25 DNA82340-2530	normal esophagus	esophageal tumor
DNA85066-2534	lung tumor normal skin	normal lung melanoma tumor
30 DNA87991-2540	esophageal tumor	normal esophagus
DNA92238-2539	normal skin	melanoma tumor
35 DNA96787-2534	normal kidney	kidney tumor

EXAMPLE 19: Identification of Receptor/Ligand Interactions

In this assay, various PRO polypeptides are tested for ability to bind to a panel of potential receptor or ligand molecules for the purpose of identifying receptor/ligand interactions. The identification of a ligand for a known receptor, a receptor for a known ligand or a novel receptor/ligand pair is useful for a variety of indications including, for example, targeting bioactive molecules (linked to the ligand or receptor) to a cell known to express the receptor or ligand, use of the receptor or ligand as a reagent to detect the presence of the ligand or receptor in a composition suspected of containing the same, wherein the composition may comprise cells suspected of expressing the ligand or receptor, modulating the growth of or another biological or immunological activity of a cell known to express or respond to the receptor or ligand, modulating the immune response of cells or toward cells that express the receptor or ligand, allowing the preparation of agonists, antagonists and/or antibodies directed against the receptor or ligand which will modulate the growth of or a biological or immunological activity of a cell expressing the receptor or ligand, and various other indications which will be readily apparent to the ordinarily skilled artisan.

The assay is performed as follows. A PRO polypeptide of the present invention suspected of being a ligand for a receptor is expressed as a fusion protein containing the Fc domain of human IgG (an immunoadhesin). Receptor-ligand binding is detected by allowing interaction of the immunoadhesin polypeptide with cells (e.g. Cos cells) expressing candidate PRO polypeptide receptors and visualization of bound immunoadhesin with fluorescent reagents directed toward the Fc fusion domain and examination by microscope.

5 Cells expressing candidate receptors are produced by transient transfection, in parallel, of defined subsets of a library of cDNA expression vectors encoding PRO polypeptides that may function as receptor molecules. Cells are then incubated for 1 hour in the presence of the PRO polypeptide immunoadhesin being tested for possible receptor binding. The cells are then washed and fixed with paraformaldehyde. The cells are then incubated with fluorescent conjugated antibody directed against the Fc portion of the PRO polypeptide immunoadhesin (e.g.

10 FITC conjugated goat anti-human-Fc antibody). The cells are then washed again and examined by microscope. A positive interaction is judged by the presence of fluorescent labeling of cells transfected with cDNA encoding a particular PRO polypeptide receptor or pool of receptors and an absence of similar fluorescent labeling of similarly prepared cells that have been transfected with other cDNA or pools of cDNA. If a defined pool of cDNA expression vectors is judged to be positive for interaction with a PRO polypeptide immunoadhesin, the

15 individual cDNA species that comprise the pool are tested individually (the pool is "broken down") to determine the specific cDNA that encodes a receptor able to interact with the PRO polypeptide immunoadhesin.

In another embodiment of this assay, an epitope-tagged potential ligand PRO polypeptide (e.g. 8 histidine "His" tag) is allowed to interact with a panel of potential receptor PRO polypeptide molecules that have been expressed as fusions with the Fc domain of human IgG (immunoadhesins). Following a 1 hour co-incubation with the epitope tagged PRO polypeptide, the candidate receptors are each immunoprecipitated with protein A beads and the beads are washed. Potential ligand interaction is determined by western blot analysis of the immunoprecipitated complexes with antibody directed towards the epitope tag. An interaction is judged to occur if a band of the anticipated molecular weight of the epitope tagged protein is observed in the western blot analysis with a candidate receptor, but is not observed to occur with the other members of the panel

25 of potential receptors.

Using these assays, the following receptor/ligand interactions have been herein identified:

- (1) PRO10272 binds to PRO5801.
- (2) PRO20110 binds to the human IL-17 receptor (Yao et al., *Cytokine* 9(11):794-800 (1997); also herein designated as PRO1) and to PRO20040.
- 30 (3) PRO10096 binds to PRO20233.
- (4) PRO19670 binds to PRO1890.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the

claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16),
5 Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54),
10 Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92),
15 Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 20 25 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) and Figure 168 (SEQ ID NO:168).

2. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 35

73 (SEQ ID NO:73), Figure 75 (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:1390), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165) and Figure 167 (SEQ ID NO:167).

3. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figure 75 (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:1390), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155),

Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165) and Figure 167 (SEQ ID NO:167).

4. Isolated nucleic acid having at least 80% nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

5

5. A vector comprising the nucleic acid of Claim 1.

6. The vector of Claim 5 operably linked to control sequences recognized by a host cell transformed with the vector.

10

7. A host cell comprising the vector of Claim 5.

8. The host cell of Claim 7, wherein said cell is a CHO cell.

15 9. The host cell of Claim 7, wherein said cell is an *E. coli*.

10. The host cell of Claim 7, wherein said cell is a yeast cell.

11. A process for producing a PRO polypeptides comprising culturing the host cell of Claim 7 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

12. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102

(SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) and Figure 168 (SEQ ID NO:168).

10

13. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

15

14. A chimeric molecule comprising a polypeptide according to Claim 12 fused to a heterologous amino acid sequence.

15. The chimeric molecule of Claim 14, wherein said heterologous amino acid sequence is an epitope tag sequence.

20

16. The chimeric molecule of Claim 14, wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

25

17. An antibody which specifically binds to a polypeptide according to Claim 12.

18. The antibody of Claim 17, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

19. Isolated nucleic acid having at least 80% nucleic acid sequence identity to:

30 (a) a nucleotide sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure

58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64),
Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID
NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ
ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88
(SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure
96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102),
Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ
ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116),
Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ
ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130),
10 Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ
ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144),
Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ
ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158),
Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ
15 ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide;

(b) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2
(SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ
ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18
(SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure
20 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32),
Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID
NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ
ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56
(SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure
25 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70),
Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID
NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ
ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94
(SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100),
30 Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ
ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114),
Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ
ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128),
Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ
35 ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142),
Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ
ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156),

WO 01/16318

Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), with its associated signal peptide; or

5 (c) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide.

20. An isolated polypeptide having at least 80% amino acid sequence identity to:

30 (a) an amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58

(SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96
5 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130),
10 Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide;

(b) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26
20 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64
25 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide;

WO 01/16318

158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), with its associated signal peptide; or

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide.

21. A method of detecting a polypeptide designated as A, B, C or D in a sample suspected of containing an A, B, C or D polypeptide, said method comprising contacting said sample with a polypeptide designated herein as E, F, G, H or I and determining the formation of a A/E, B/F, B/G, C/H or D/I polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of an A, B, C or D polypeptide in said sample and wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

35

22. The method according to Claim 21, wherein said sample comprises cells suspected of expressing said A, B, C or D polypeptide.

23. The method according to Claim 21, wherein said E, F, G, H or I polypeptide is labeled with a detectable label.

24. The method according to Claim 21, wherein said E, F, G, H or I polypeptide is attached to a solid support.

5

25. A method of detecting a polypeptide designated as E, F, G, H or I in a sample suspected of containing an E, F, G, H or I polypeptide, said method comprising contacting said sample with a polypeptide designated herein as A, B, C or D and determining the formation of a A/E, B/F, B/G, C/H or D/I polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of an A, B, C or D polypeptide in said sample and wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

10 26. The method according to Claim 25, wherein said sample comprises cells suspected of expressing said E, F, G, H or I polypeptide.

15

27. The method according to Claim 25, wherein said A, B, C or D polypeptide is labeled with a detectable label.

20 28. The method according to Claim 25, wherein said A, B, C or D polypeptide is attached to a solid support.

25 29. A method of linking a bioactive molecule to a cell expressing a polypeptide designated as A, B, C or D, said method comprising contacting said cell with a polypeptide designated as E, F, G, H or I that is bound to said bioactive molecule and allowing said A, B, C or D and said E, F, G, H or I polypeptides to bind to one another, thereby linking said bioactive molecules to said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

30

30. The method according to Claim 29, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

35 31. The method according to Claim 29, wherein said bioactive molecule causes the death of said cell.

32. A method of linking a bioactive molecule to a cell expressing a polypeptide designated as E, F, G, H or I, said method comprising contacting said cell with a polypeptide designated as A, B, C or D that is bound to said bioactive molecule and allowing said A, B, C or D and said E, F, G, H or I polypeptides to bind to one another, thereby linking said bioactive molecules to said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

5 33. The method according to Claim 32, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

10 34. The method according to Claim 32, wherein said bioactive molecule causes the death of said cell.

15 35. A method of modulating at least one biological activity of a cell expressing a polypeptide designated as A, B, C or D, said method comprising contacting said cell with a polypeptide designated as E, F, G, H or I or an anti-A, B, C or D polypeptide antibody, whereby said E, F, G, H or I polypeptide or anti-A, B, C or D polypeptide antibody binds to said A, B, C or D polypeptide, thereby modulating at least one biological activity of said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

20 36. The method according to Claim 35, wherein said cell is killed.

25 37. A method of modulating at least one biological activity of a cell expressing a polypeptide designated as E, F, G, H or I, said method comprising contacting said cell with a polypeptide designated as A, B, C or D or an anti-E, F, G, H or I polypeptide antibody, whereby said A, B, C or D polypeptide or anti-E, F, G, H or I polypeptide antibody binds to said E, F, G, H or I polypeptide, thereby modulating at least one biological activity of said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

30 38. The method according to Claim 37, wherein said cell is killed.

FIGURE 1

GGGGCTCGGCCAGCGCTAGTCGGCTGGTAAGGATTCACAAAGGTGCAGGTA
TGAGCAGGTCTGAAGACTAACATTGTGAAGTGTAAAACAGAAAACCTGTTAGAA**ATGT**GG
TGGTTTCAGCAAGGCCTCAGTTCCCTTCAGCCCTGTAATTGGACATCTGCTGCTTTC
ATATTTCATACATTACTGCAGTAACACTCCACCATAGACCCGGCTTACCTTATATCAGT
GACACTGGTACAGTAGCTCCAGAAAAATGCTTATTGGGGCAATGCTAAATATTGCGGCAGTT
TTATGCATTGCTACCATTATGTTGTTATAAGCAAGTTCATGCTCTGAGTCCTGAAGAGAAC
GTTATCATCAAATTAAACAAGGCTGGCTTGACTTGGAAATACTGAGTTGTTAGGACTTTCT
ATTGTGGCAAACCTCCAGAAAACAACCCCTTTGCTGCACATGTAAGTGGAGCTGTGCTTACC
TTGGTATGGGCTCATTATATATGTTGTTCAGACCATCCTCCTACCAAATGCAGCCAAA
ATCCATGGCAAACAAGTCTTCTGGATCAGACTGTTGGTTATCTGGTGTGGAGTAAGTGC
CTTAGCATGCTGACTGCTCATCAGTTGCACAGTGGCAATTGGGACTGATTAGAACAG
AAACCTCCATTGGAACCCCGAGGACAAAGGTTATGTGCTTCACATGATCACTACTGCAGCAGAA
TGGTCTATGTCATTTCCTCTTGGTTTTCTGACTTACATTGATTTCAGAAAATT
TCTTACGGGTGGAAGCCAATTACATGGATTAACCCCTATGACACTGCACCTGCCCTATT
AACAAATGAACGAACACGGCTACTTCCAGAGATATT**TGA**TGAAAGGATAAAATATTCTGTAA
TGATTATGATTCTCAGGGATTGGGAAAGGTTCACAGAAGTTGCTTATTCTCTGAAATT
TCAACCACTTAATCAAGGCTGACAGTAACACTGATGAATGCTGATAATCAGGAAACATGAAAG
AAGCCATTGATAGATTATTCTAAAGGATATCATCAAGAAGACTATTAAAAACACCTATGCCT
ATACTTTTATCTCAGAAAATAAGTCAAAAGACTATG

FIGURE 2

<subunit 1 of 1, 266 aa, 1 stop

<MW: 29766, pI: 8.39, NX(S/T): 0

MWWFQQGLSFLPSALVIWTSAAFIFSYITAVTLHHIDPALPYISDTGTVAPEKCLFGAMLNIA
AVLCIATIYVRYKQVHALSPEENVIKLNKAGLVLGILSCLGLSIVANFQKTLFAAHVSGAV
LTFGMGSLYMFVQTILSYQMOPKIHGKQVFWIRLLLVIWCGVSALSMTCSSVLHSGNFGTDL
EQKLHWNPEDKGYVLHMITTAAEWSMSFSFFGFLTYIRDFQKISLRVEANLHGLTLYDTAPC
PINNERTRLLSRDI

Important features:

Type II transmembrane domain:

amino acids 13-33

Other Transmembrane domains:

amino acids 54-73, 94-113, 160-180, 122-141

N-myristoylation sites.

amino acids 57-63, 95-101, 99-105, 124-130, 183-189

FIGURE 3

CGGACGCGTGGCGGACGCGTGGGGAGAGCCGCAGTCCGGCTGCAGCACCTGGAGAAGGC
AGACCGTGTGAGGGGGCTGTGGCCCCAGCGTGTGCAGCTGGGGAGTGGGAAGTGGAGGC
AGGAGCCTCCTTACACTTCGCCATGAGTTCTCATCGACTCCAGCATCATGATTACCTCCC
AGATACTATTTGGATTGGCTTCTCATGCCAATTGTTAAAGACTATGAGA
TACGTCAGTATGTTGTACAGGTGATCTTCTCCGTGACGTTGCATTTCTGCACCATGTTG
AGCTCATCATCTTGAAATCTAGGAGTATTGAATAGCAGCTCCGTTATTTCACTGGAAA
TGAACCTGTGTGAATTCTGCTGATCCTGGTTCTCATGGGCCTTTACATTGGCTATTTA
TTGTGAGCAATATCCGACTACTGCATAAACAAACGACTGCTTTCTGTCTTATGGCTGA
CCTTATGTATTCCTGGAAACTAGGAGATCCCTTCCATTCTCAGCCAAAACATGGGA
TCTTATCCATAGAACAGCTCATGCCGGTTGGTGTGATTGGAGTGACTCTCATGGCTTTC
TTTCTGGATTGGTGTCAACTGCCATACACTACATGTCTTACCTCAGGAATGTGA
CTGACACGGATTCTAGCCCTGGAACGGCAGTGTGCAAACCATGGATATGATCATAAGCA
AAAAGAAAAGGATGGCAATGGCACGGAGAACAAATGTTCCAGAAGGGGAAGTGCATAACAAAC
CATCAGGTTCTGGGAATGATAAAAAGTGTACCAACTTCAGCATCAGGAAGTGAAAATCTTA
CTCTTATTCAACAGGAAGTGGATGCTTGGAAAGAATTAAGCAGGCAGCTTTCTGGAAACAG
CTGATCTATATGCTACCAAGGAGAGAACAGAACACCTCAAGGGAAATATTTA
ATTTCTGGTTACTTTCTCTATTACTGTGTTGGAAAATTTCATGGCTACCATCAATA
TTGTTTTGATCGAGTTGGAAAACGGATCCTGTCACAAGAGGCATTGAGATCACTGTGAATT
ATCTGGGAATCCAATTGATGTGAAGTTGGTCCAAACACATTCCCTCATTCTGGAA
TAATCATCGTCACATCCATCAGAGGATTGCTGATCAGTCTTACCAAGTTCTTATGCCATCT
CTAGCAGTAAGTCCCAATGTCATTGCTGCTATTAGCACAGATAATGGCATGTACTTG
TCTCCTCTGTGCTGCTGATCCGAATGAGTATGCCTTAGAATACCGCACCATAACTGAAG
TCCTGGAGAACTGCAGTTCAACTCTATCACCGTTGGTTGATGTGATCTCCTGGTCAGCG
CTCTCTCTAGCATACTCTCCTCTATTGGCTCACAAACAGGCACCAGAGAACAAATGGCAC
CTTGAACTTAAGCCTACTACAGACTGTTAGAGGCCAGTGGTTCAAAATTAGATATAAGAGG
GGGGAAAATGGAACCAGGGCCTGACATTATAAACAAACAAATGCTATGGTAGCATT
CACCTCATAGCATACTCCTCCCCGTAGGTGATACTATGACCATGAGTAGCATGCCAGA
ACATGAGAGGGAGAACACTAACAGACAATACTCAGCAGAGAGCATCCGTGTGGATATGAGG
CTGGTGTAGAGGCAGAGGGAGGCCAGAACACTAAAGGTGAAAATACACTGGAACCTGGGGC
AAGACATGTCTATGGTAGCTGAGCCAAACACGTAGGATTCCGTTAAGGTTCACATGGAAA
AGGTTATAGCTTGCCTTGAGATTGACTCATTAAACAGAGACTGTAACAAAAAA
AAAAAAAGGGCGGCCGCGACTCTAGAGTCGACCTGCAGAAGCTGGCCCATGGCCAACT
TGTTTATTGCAGCTTATAATG

FIGURE 4

MSFLIDSSIMITSQILFFFGFWLFFMRQLFKDYEIRQYVVQVIFSVTFAFSCTMFELIIFEIL
GVLNSSSRYFHWKMNLCVILLILVFMVPFYIGYFIVSNIRLLHKQRLLFSCLLWLTFMYFFWK
LGDPFPILSPKKGILSIEQLISRGVIGVTLMALLSGFGAVNCPTYMSYFLRNVTDTDILAL
ERRLLQTMDMIISKKKRMAMARRTMFQKGEVHNKPSGFWMKSVTTSASGSENLTLIQQEVD
ALEELSRLFLETADLYATKERIEYSKTFKGKYFNFLGYFFSIYCVWKIFMATINIVFDRV GK
TDPVTRGIEITVNYLGIQFDVKFWSQHISFILVGIIIVTSIRGLLITLTKFFYAISSSKSSNV
IVLLLAQIMGMYFVSSVLLIRMSMPLYRTIITEVLGELQNFYHRWFDVIFLVSALSSILFL
YLAHKQAPEKQMAP

Important features:

Signal peptide:

amino acids 1-23

Potential transmembrane domains:

amino acids 37-55, 81-102, 150-168, 288-311, 338-356, 375-398,
425-444

N-glycosylation sites.

amino acids 67-70, 180-183 and 243-246

Eukaryotic cobalamin-binding proteins

amino acids 151-160

FIGURE 5

AGCAGGGAAATCCGGATGTCGGTTATGAAGTGGAGCAGTGAGTGTGAGCCTAACATAGTT
CCAGAACTCTCCATCCGGACTAGTTATTGAGCATTGAGCAGTGAGCCTAACATAGCTG
AGGTGTTCCCTGGCTCTGAAGGGTAGGCACG**ATGCCAGGTGCTTCAGCCTGGTGTGCTT**
CTCACTTCCATCTGGACCACGAGGCTCCTGGTCCAAGGCTCTTGCGTGAGAAGAGCTTCC
ATCCAGGTGTCACTGCAGAATTATGGGGATCACCTTGTGAGCAAAAAGGCGAACAGCAGCTG
AATTTCACAGAAGCTAAGGAGGCCTGTAGGCTGCTGGGACTAAGTTGGCCGGCAAGGACCAA
GTTGAAACAGCCTGAAAGCTAGCTTGAAACTTGAGCTATGGCTGGGTTGGAGATGGATT
GTGGTCATCTCTAGGATTAGCCAAACCCAAAGTGTGGGAAAAATGGGGTGGGTGCTGATT
TGGAAAGGTCCAGTGAGCCACAGTTGCAGCCTATTGTTACAACACTGATACTGGACT
AACTCGTCATTCCAGAAATTATCACCACCAAAGATCCCATTCAACACTCAAACACTGCAACA
CAAACAAACAGAATTATTGTCACTGACAGTACCTACTCGGTGGCATCCCCTACTCTACAATA
CCTGCCCTACTACTACTCCTCCTGCTCCAGCTTCACTTCTATTCCACGGAGAAAAAATTG
ATTGTGTACAGAAGTTTATGGAAACTAGCACCAGTCTACAGAAACTGAACCATTGTT
GAAAATAAAGCAGCATTCAAGAATGAAGCTGCTGGGTTGGAGGTGTCCCCACGGCTCTGCTA
GTGCTTGCTCTCCTCTTGGTGCAGCTGGTCTGGATTGTCTATGTCAAAAGGTAT
GTGAAGGCCTCCCTTTACAAACAAGAATCAGCAGAAGGAATGATGAAACCAAAGTAGTA
AAGGAGGAGAAGGCCAATGATAGCAACCCATAATGAGGAATCAAAGAAAATGATAAAAACCA
GAAGAGTCCAAGAGTCCAAGCAAAACTACCGTGCATGCCTGGAAGCTGAAGT**TAGATGAGA**
CAGAAATGAGGAGACACACCTGAGGCTGGTTCTTCATGCTCCTACCCCTGCCAGCTGGG
GAAATCAAAGGGCAAAGAACCAAAGAAGAAAGTCCACCCCTGGTCTAACTGGAATCAGC
TCAGGACTGCCATTGGACTATGGAGTGCACCAAAGAGAATGCCCTCTCCTTATTGTAACCC
GTCTGGATCCTATCCTCCTACCTCCAAAGCTTCCCACGGCCTTCTAGCCTGGCTATGCTA
ATAATATCCCCTGGAGAAAGGAGTTTGCAAAGTGCAGGACCTAAACATCTCATCAGTA
TCCAGTGGTAAAAGGCCTCCTGGCTGTCTGAGGCTAGGTGGGTTGAAAGCCAAGGAGTC
GAGACCAAGGCTTCTACTGATTCCGAGCTCAGACCCCTTCTCAGCTCTGAAAGAGAAA
CACGTATCCCACCTGACATGCTTCTGAGCCGGTAAGAGCAAAAGAATGGCAGAAAAGTT
AGCCCCTGAAAGCCATGGAGATTCTCATAACTTGAGACCTAATCTGTAAAGCTAAAATAAA
GAAATAGAACAGGCTGAGGATACGACAGTACACTGTCAGCAGGGACTGTAACACAGACAGG
GTCAAAGTGTGTTCTGAACACATTGAGTGGATCACTGTTAGAACACACACTTACTT
TTCTGGTCTCTACCACTGCTGATATTTCTAGGAAATATACTTTACAAGTAACAAAAT
AAAAACTCTTATAAATTCTATTTTATCTGAGTTACAGAAATGATTACTAAGGAAGATTACT
CAGTAATTGTTAAAAGTAATAAAATTCAACAAACATTGCTGAATAGCTACTATATGTCA
AGTGCTGTGCAAGGTATTACACTCTGTAATTGAATATTATTCTCAAAAATTGCACATAGTA
GAACGCTATCTGGGAAGCTATTTTCTAGTTGATATTCTAGCTATCTACTTCCAAACT
AATTTTATTTGCTGAGACTAATCTTATTCTATTCTCAATATGGCAACCATTATAACCT
TAATTATTATAACATACCTAAGAAGTACATTGTTACCTCTATATACCAAGCACATTAA
AAGTGCCATTAACAAATGTACTAGCCCTCTTTCCAACAAGAAGGGACTGAGAGATGC
AGAAATATTGTGACAAAAAATTAAAGCATTAGAAAACCTT

6/168

FIGURE 6

MARCFSLVLLLTSIWTTRLLVQGSLRAEELSIQVSCRIMGITLVSKKANQQLNFTEAKEACRL
LGLSLAGKDQVETALKASFETCSYGVGDGFVVISRISPNSPKCGKNGVGVLIWKVPVSRQFAA
YCYNSSDTWTNSCIPEIITTKDPIFNTQTATQTTEFIVSDSTYSVSPYSTIPAPTPPPAPA
STSIPRRKKLICVTEVFMETSTMSTETEPFVENKAAFKNEAAGFGGVPTALLVLALLFFGAAA
GLGFCYVKRYVKAFPFTNKNQQKEMIETKVVKEEKANDSNPNEESKTDKNPEESKSPSKTTV
RCLEAEV

Signal sequence:

amino acids 1-16

Transmembrane domain:

amino acids 235-254

N-glycosylation site.

amino acids 53-57, 130-134, 289-293

Casein kinase II phosphorylation site.

amino acids 145-149, 214-218

Tyrosine kinase phosphorylation site.

amino acids 79-88

N-myristoylation site.

amino acids 23-29, 65-71, 234-240, 235-239, 249-255, 253-259

FIGURE 7

CGCCGCGCTCCGCACCGCGGCCCGCCCACCGCGCCGCTCCGCATCTGCACCCGAGCCCG
GCGGCCTCCGGCGGGAGCGAGCAGATCCAGTCCGGCCCGCAGCGCAACTCGGTCCAGTCGGG
GCGGCGGCTCGGGCGCAGAGCGGAGATGAGCAGCGCTGGGCTGGGCCACCCCTGCTGTGCCTGCTGC
TGGCGGCGGCGGTCCCCACGGCCCCCGCGCCGCTCCGACGGCGACCTCGGCTCCAGTCAAGC
CCGGCCCAGCTCTCAGCTACCGCAGGAGGAGGCCACCTCAATGAGATGTTCCGCGAGGTTG
AGGAAGTGTGGAGGACACGCAGCACAAATTGCGCAGCGCGGTGGAAGAGATGGAGGCAGAAG
AAGCTGCTGCTAAAGCATCATCAGAAGTGAACCTGGCAAACCTACCTCCAGCTATCACAATG
AGACCAACACAGACACGAAGGTTGAAATAATACCATCCATGTGCACCGAGAAATTACAAGA
TAACCAACAAACCAGACTGGACAAATTGGCTTTCAGAGACAGTTATCACATCTGTGGAGACG
AAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACGAGGACTGTGGGCCAGAGGATGCTCTGCACCCGGG
AGTTGCCAGCTCCAGTACACCTGCCAGCCATGCCGGGGCAGAGGATGCTCTGCACCCGGG
ACAGTGAGTGTGGAGACAGCTGTGTCTGGGACTGCACCCAGGAGCTGGGAGGAGACG
GCAGCAATGGGACCATCTGTGACAACCAGAGGGACTGCCAGCCGGGCTGTGCTGCTTCC
AGAGAGGCCTGCTGTTCCCTGTGCACACCCCTGCCCGTGGAGGGCAGAGGATTTGCCATGACC
CCGCCAGCCGGCTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGAT
GCCCTTGTGCCAGTGGCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGCAAGC
CGACCTTCGTGGGAGCCGTGACCAAGATGGGAGATCCTGCTGCCAGAGGGTCCCCGATG
AGTATGAAGTTGGCAGCTTCATGGAGGGAGGTGCGCCAGGAGCTGGAGGACCTGGAGAGGAGCC
TGAAGAGAGATGGCGCTGGGGAGCCTGCCAGGGCTGCCGCCGTGCAGTGTGGAGGGGAAG
AGATT**TAG**ATCTGGACCAAGGCTGTGGTAGATGTGCAATAGAAATAGCTAATTATTC
GGTGTGTGCTTGGCGTGGCTGACCAGGCTTCTCCTACATCTTCTCCAGTAAGTTCC
CCTCTGGCTTGACAGCATGAGGTGTTGTGCATTGTCAGCTCCCCCAGGCTGTTCTCAGGC
TTCACAGTCTGGTCTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTGCCACCCCT
GTCCAGATTATTGGCTGCTTGCCTCTACCAAGTTGGCAGACAGCCGTTGTTCTACATGGCTT
TGATAATTGTTGAGGGAGGGAGATGGAAACAATGTGGAGTCTCCCTCTGATTGGTTGGGG
AAATGTGGAGAAGAGGTGCCCTGCTTGAAACATCAACCTGGAAAAATGCAACAAATGAATT
TTCCACGCAGTTCTTCCATGGCATAGGTAAGCTGTGCCTCAGCTGTTGCAAGATGAAATGT
TCTGTTCACCTGCATTACATGTGTTATTGTCAGCAGTGTGCTCAGCTCCTACCTCTGT
GCCAGGGCAGCATTTCATATCCAAGATCAATTCCCTCTCAGCACAGCCTGGGGAGGGGGT
CATTGTTCTCCTCGTCCATCAGGGATCTCAGAGGCTCAGAGACTGCAAGCTGCTGCCAAGT,
CACACAGCTAGTGAAGACCAGAGCAGTTCATCTGGTTGTGACTCTAAGCTCAGTGTCTCTC
CACTACCCACACCAAGCCTGGTGCCACAAAAGTGTCCCCAAAAGGAAGGAGAATGGGATT
TTCTTGAGGCATGCACATCTGAAATTAGGTCAAACATATTCTCACATCCCTCTAAAGTAA
ACTACTGTTAGGAACAGCAGTGTCTCACAGTGTGGGGAGCCGTCTTCTAATGAAGACAAT
GATATTGACACTGTCCCTCTTGGCAGTTGCATTAGTAACTTGAAAGGTATATGACTGAGCG
TAGCATACAGGTTAACCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGA
AATTGCAAATCACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACC
GAGCAGGGCTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACACTACGCCACTC
CACAAATGATGTTTCAGGTGTCACTGGACTGTGCTCAGAGCTGGTCTTAAATTATGTATAAACAT
GTTTAAAGTTGCACATGATTGATAAGCATGCTTCTTGTAGTTAAATTATGTATAAACAT
AAGTTGCATTAGAAATCAAGCATAAAACTCACTCAACTGCAAAAAAAAAAAAAAAA
AAA

FIGURE 8

MQRLGATLLCLLLAAAVPTAPAPAPTATSAPVKPGPALSYPQEEATLNEMFREVEELMEDTQH
KLRSAVEEEMEAEEAAKASSEVNLANLPPSYHNETNTDTKVGNNTIHVHREIHKITNNQTGQM
VFSETVITSVGDEEGRRSHECI IDEDCGPSMYCQFASFQYTCQPCRGQRMLCTRSECCGDQL
CVWGHCTKMATRGSGNTICDNQRDCQPGLCCAFQRGLLFPVCTPLPVEGELCHDPASRLLDLI
TWELEPDGALDRCPCASGLLCQPHSHSLVYVCKPTFVGSRDQDGEILLPREVPDEYEVGSFME
EVRQELEDLERSLTEEMALGEAAAAALLGEEI

Signal sequence:

amino acids 1-19

N-glycosylation site.

amino acids 96-100, 106-110, 121-125, 204-208

Casein kinase II phosphorylation site.

amino acids 46-50, 67-71, 98-102, 135-139, 206-210, 312-316,
327-331

N-myristoylation site.

amino acids 202-208, 217-223

Amidation site.

amino acids 140-144

FIGURE 9

CGGACGCGTGGCGGACGCGTGGGGCTGTGAGAAAGTCCAATAAACATCATGCAACCCC
ACGGCCCACCTTGTGAACTCCTCGTGCCAGGGCTGATGTGCGTCTCCAGGGCTACTCATCC
AAAGGCCTAATCCAACGTTCTGTCTCAATCTGAAATCTATGGGTCTGGGGCTTCTGG
ACCCTTAACGGTACTGCCCTGGCCAATGCGCCTCGCTGGAGCCTTGCCTCCTCTAC
TGGGCTTCCACAAGCCCCAGGACATCCCTACCTCCCTTAATCTCTGCCTCATCCGACA
CTCCGTTACCACACTGGTCATTGGCATTGGAGGCCATCCTGACCCCTGTGCAGATAGCC
CGGGTCATCTGGAGTATATTGACCACAAGCTCAGAGGAGTGCAGAACCCCTGTAGCCGCTGC
ATCATGTGCTGTTCAAGTGCTGCCTCTGGTGTCTGGAAAAATTATCAAGTTCTAAACCGC
AATGCATACATCATGATGCCATCTACGGGAAGAATTCTGTGTCTCAGCCAAAATGCGTTC
ATGCTACTCATGCGAACATTGTCAGGGTGGTCGTCTGGACAAAGTCACAGACCTGCTGCTG
TTCTTGGGAAGCTGCTGGTGGCGAGGCGTGGGGCTGTCTTTCTCCGGT
CGCATCCCGGGCTGGTAAAGACTTTAAGAGCCCCACCTCAACTATTACTGGCTGCCATC
ATGACCTCCATCCTGGGGCCTATGTCATGCCAGCGGCTTCTCAGCGTTTCCGGATGTGT
GTGGACACGCTTCCCTCTGCTTGGAGACCTGGAGCGGAACAACGGCTCCCTGGACCGG
CCCTACTACATGTCCAAGAGCCTTCTAAAGATTCTGGCAAGAAGAACGAGGCGCCCCGGAC
AACAAAGAGAGGAAGAAGTGACAGCTCCGGCCCTGATCCAGGACTGCACCCACCCCGT
CCAGCCATCCAACCTCACTCGCCTTACAGGTCTCCATTGTGGTAAAAAGGTTTAGGC
CAGGCGCCGTGGCTACGCCTGTAATCCAACACTTGAGAGGCTGAGGCAGGCGGATCACCTG
AGTCAGGAGTTGAGACCAGCCTGGCAACATGGTAAACCTCCGTCTCTATTAAAAATACAA
AAATTAGCCGAGAGTGGTGGCATGCACTGTCACTCCAGCTACTCGGGAGGCTGAGGCAGGAG
AATCGCTTGAACCCGGAGGCAGAGGTTGCAGTGAGCCGAGATCGCGCCACTGCACTCCAACC
TGGGTGACAGACTCTGTCTCCAAAACAAACAAACAAAAGATTATTAAAGATATT
TGTAACTC

10/168

FIGURE 10

RTRGRTRGGCEKVPINTSCNPTAHVNSSCPGLMCVFQGYSSKGLIQRSVFNLQIYGVLGLFW
TLNWVLALGQCVLAGAFASFYWAFHKPQDIPTFPLISAFIRTLRYHTGSLAFGALILTLVQIA
RVILEYIDHKLRGVQNPVARCIMCCFKCCLWCLEKFIKFLNRNAYIMIAIYGKNFCVSAKNAF
MLLMRNIVRVVVLVDKVTDLLFFGKLLVVGVGVLSSFFSGRIPGLGKDFKSPHLNYYWLPI
MTSILGAYVIASGFFSVFGMCVDTLFLCFLEDLERNNNGSLDRPYYMSKSLKILGKKNEAPPD
NKKRKK

Important features:

Transmembrane domains:

amino acids 57-80 (type II), 110-126, 215-231, 254-274

N-glycosylation sites.

amino acids 16-20, 27-31, 289-293

Hypothetical YBR002c family proteins.

amino acids 276-288

Ammonium transporters proteins.

amino acids 204-231

N-myristoylation sites.

amino acids 60-66, 78-84

Amidation site.

amino acids 306-310

11/168

FIGURE 11

GCCCGCGCCCGGCCGGCGCCGGCGCCGAAGCCGGAGCCACCGCC **ATGGGGCCTGCCTGGAG**
CCTGCTCCCTGCTCAGCTGCGCGTCTGCCTCTGCAGCTCTGCCTGCATCCTGTGCAGCT
GCTGCCCGCCAGCCAACTCCACCGTGAGCCGCCTCATCTCACGTTCTTCCTCTCCTGG
GGGTGCTGGTGTCCATCATTATGCTGAGCCCGGGCGTGGAGAGTCAGCTCTACAAGCTGCCCT
GGGTGTGTGAGGAGGGGCCGGATCCCCACCGTCCTGCAGGGCACATCGACTGTGGCTCCC
TGCTTGGCTACCGCGTGTCTACCGCATGTGCTTCGCCACGGCGCCTCTTCTTCTTCTT
TCACCCCTGCTCATGCTCTGCGTGAGCAGCAGCCGGACCCCCGGGCTGCCATCAGAATGGGT
TTTGGTTCTTAAGTTCTGATCCTGGTGGCCTCACCGTGGTGCCTCTACATCCCTGACG
GCTCCTCACCAACATCTGGTTCTACTTCGGCGTGTGGCTCCTCTTCTTACATCCTCATCC
AGCTGGTGCTGCTCATCGACTTGCACACTCCTGGAACCAGCGGTGGCTGGCAAGGCCGAGG
AGTGCATTCCCGTGCCTGGTACGCAGGCCTCTTCTTCACTCTCCTCTTACTTGCTGT
CGATCGCGGCCGTGGCGCTGATGTTCATGTACTACACTGAGCCCAGCGGCTGCCACGAGGGCA
AGGTCTTCATCAGCCTCAACCTCACCTCTGTGTCTGCGTGTCCATCGCTGCTGTCCTGCCA
AGGTCCAGGACGCCAGCCAACTCGGTCTGCTGCAGGCCTCGGTATCACCCCTACACCA
TGTTTGTACCTGGTCAGCCCTATCCAGTATCCCTGAACAGAAATGCAACCCCCATTGCCAA
CCCAGCTGGCAACGAGACAGTTGTGGCAGGCCCGAGGGCTATGAGACCCAGTGGTGGGATG
CCCCGAGCATTGTGGCCTCATCATCTTCCTGTGCACCCCTTCATCAGTCTGCGCTCCT
CAGACCACCGCAGGTGAACAGCCTGATGCAGACCGAGGAGTGCCACCTATGCTAGACCCA
CACAGCAGCAGCAGCAGCAGGTGGCAGCCTGTGAGGGCCGGGCTTGACAAACGAGCAGGACG
GCGTCACCTACAGCTACTCCTCTTCACTCTGCCTGGTGTGGCTCACTGCACGTCACTGA
TGACGCTACCAACTGGTACAAGCCGGTGAGACCCGGAAAGATGATCAGCACGTGGACCCCG
TGTGGGTGAAGATCTGTGCCAGCTGGCAGGGCTGCTCCTTACCTGTGGACCCCTGGTAGCCC
CACTCCTCTGCGCAACCGCGACTTCAGC **TCA**AGGCAGCCTCACAGCCTGCCATCTGGTGCCTC
CTGCCACCTGGTGCCTCTGGCTCGGTGACAGCCAACCTGCCCTCCCCACACCAATCAGCC
AGGCTGAGCCCCACCCCTGCCAGCTCCAGGACCTGCCCTGAGCCGGGCTTAGTCGT
AGTGCCTTCAGGGTCCGAGGAGCATCAGGCTCCTGCAGAGCCCCATCCCCCGCCACACCCAC
ACGGTGGAGCTGCCCTTCCTCCCTCTGGTGTGGCTAGCAGCATCTCGGATGAAA
GGGCTCCCTTGTCTCAGGCTCCAGGGAGCGGGCTGCTGGAGAGAGCGGGAACTCCCACC
ACAGTGGGGCATCCGGCACTGAAGCCCTGGTGTTCCTGGTACGTCCCCAGGGGACCCCTGCC
CCCTCCTGGACTCGTGCCTTAAGACTTTCTAATAAACAGCCAGTGCG
TGTAAAAAAA

12/168

FIGURE 12

MGACLGACSLSCASCLCGSAPCILCSCCPASRNSTVSRLIFTFFLFLGVLVSIIMLSPGVES
OLYKLPWVCEEGAGIPTVLQGHIDCGSLLGYRAVYRMCATAAFFFFFFTLLMLCVSSSRDPR
AAIQNGFWFFKFLILVGLTVGAFYIPDGSFTNIWFYFGVVGSFLFILIQLVLLIDFAHSWNQR
WLGKAEECDSRAWYAGLFFFTLLFYLLSIAAVALMFMYYTEPSGCHEGKVFISLNLTFCVCVS
IAAVLPKVQDAQPNGLLQASVITLYTMFVTWSALSSIPEQKCNPHLPTQLGNETVVAGPEGY
ETQWWDAPSIVGLIIFLLCTLFISLRSSDHRQVNLSLMQTEECPPMLDATQQQQQQVAACEGRA
FDNEQDGVTYSYSFFHFCLVLASLHVMMTLTNWYKPGTRKMISTWTAVWVKICASWAGLLY
LWTLVAPLLLNRNDFS

Signal sequence:

amino acids 1-20

Transmembrane domains:

amino acids 40-58, 101-116, 134-150, 162-178, 206-223, 240-257,
272-283, 324-340, 391-406, 428-444

FIGURE 13

CGGGCCAGCCTGGGGCGGCCGGCCAGGAACCACCCGTTAAGGTGTCTCTTTAGGGATGGT
GAGGTTGGAAAAAGACTCCTGTAACCCCTCCAGGATGAACCACCTGCCAGAAGACATGGAG
AACGCTCTCACCGGGAGCCAGAGCTCCATGCTTCTGCGCAATATCCATTCCATCAACCCC
ACACAACATCATGGCCAGGATTGAGTCCTATGAAGGAAGGGAAAAGAAAGGCATATCTGATGTC
AGGAGGACTTCTGTTGTTGTCACCTTGACCTCTTATTGTAACATTACTGTGGATAATA
GAGTTAAATGTGAATGGAGGCATTGAGAACACATTAGAGAAGGGAGGTGATGCAGTATGACTAC
TATTCTCATATTTGATATATTCTCTGGCAGTTTCGATTAAAGTGTAAACTTGCAC
TATGCTGTGTCAGACTGCCATTGGTGGCAATAGCGTTGACAACGGCAGTGACCAGTGCC
TTTTACTAGCAAAAGTGATCCTTCGAAGCTTTCTCAAGGGGCTTGGCTATGTGCTG
CCCATCATTTCATTCATCCTGCCTGGATTGAGACGTGGTCCTGGATTCAAAGTGTACCT
CAAGAACAGAAGAACAGACTCCTGATAGTCAGGATGCTCAGAGAGGGCAGCACTT
ATACCTGGTGGCTTCTGATGGTCAGTTTATTCCCTCCTGAATCCGAAGCAGGATCTGAA
GAAGCTGAAGAAAACAGGACAGTGAGAACCACTTTAGAACTATGAGTACTACTTTGTTA
AATGTGAAAACCCCTCACAGAAAGTCATCGAGGCAGGAGGAGGTGGAGTCTCCCTG
TCGACAGTAAGTTGAAATGGTACGTCCACTGCTGGCTTATTGAACAGCTAATAAGATT
ATTATTGTAATACCTCACAAACGTTGACCATATCCATGCACATTAGTTGCCTGCCTGTGG
CTGGTAAGGTAATGTCATGATTCATCCTCTCTCAGTGAGACTGAGCCTGATGTGTTAACAAA
TAGGTGAAGAAAGTCTTGTGCTGTATTCTAATCAAAAGACTTAATATATTGAAGTAACACTT
TTTAGTAAGCAAGATACTTTTATTCAATTCACAGAATGGAATTTTTGTTCATGTCT
CAGATTATTGTATTCTTTAACACTCTACATTCCCTGTTTTAACATGCACA
TGTGCTCTTGTACAGTTAAAAGTGTAAATAAAATCTGACATGTCAATGTGGCTAGTTA
TTTTCTTGTGTTGCATTATGTGTATGGCCTGAAGTGGACTTGCAAAAGGGAAAGAAAGG
AATTGCGAATACATGTAAAATGTCACCAGACATTGTATTATTATCATGAAATCATGTT
TTCTCTGATTGTTCTGAAATGTTCTAAATACTCTTATTGAAATGCACAAAATGACTAAACC
ATTCATATCATGTTCTTGCCTGCAGCCAATTCAATTAAATGAACAAATTAAAAAA

14/168

FIGURE 14

MNHLPEDMENALTGSQSSHASLRNIHSINPTQLMARIESYEGREKKGISDVRRTFCLFVTFDL
LFVTLLWIIELNVNGGIENTLEKEVMQYDYYSSYFDIFLLAVFRFKVLILAYAVCRLRHWWAI
ALTTAVTSAFLLAKVILSKLFSQGAFGYVLPIISFILAWIETWFLDFKVLQPQEAEENRLLIV
QDASERAALIPGGLSDGQFYSPPESEAGSEEAEEKQDSEKPLLEL

Important features of the protein:

Signal peptide:

amino acids 1-20

Transmembrane domains:

amino acids 54-72, 100-118, 130-144, 146-166

N-myristoylation sites.

amino acids 14-20, 78-84, 79-85, 202-208, 217-223

FIGURE 15

ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCTCGGGCCCGACCCGCCAGGAAAGACTGA
GGCCGCGGCCCTGCCCGCCGGCTCCCTGCGCCGCCGCCCTCCCGGGACAGAAG**ATG**TGCT
C³AGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCTGGGGTGCAGGGCT
GCCCATCCGGCTGCCAGTGCAGCCACAGACAGTCTTCTGCACTGCCGCCAGGGGACCA
CGGTGCCCGAGACGTGCCACCCGACACGGTGGGCTGTACGTCTTGAGAACGGCATCACCA
TGCTCGACGCAGGCAGCTTGCCGGCTGCCGGGCTGCAGCTCCTGGACCTGTCACAGAAC
AGATGCCAGCCTGCCAGCGGGTCTTCAGCCACTGCCAACCTCAGCAACCTGGACCTGA
CGGCCAACAGGCTGCATGAAATACCAATGAGACCTTCCGTGGCCTGCCGCCTGAGCGCC
TCTACCTGGCAAGAACCGCATCCGCCACATCCAGCCTGGTGCCTCGACACGCTGACCGCC
TCCCTGGAGCTCAAGCTGCAGGACAACAGAGCTGCCACTGCCCTGGAGGCCGATCCTGGACACTG
TGCTGCTGCTGGACCTCAGCCACAACAGCCTCCTGGCCCTGGAGGCCGCTGCCCTGCC
CCAACGTGGAGGCCTGCCCTGGCTGGTCTGGGCTGCAGCAGCTGGACGAGGGCTTTCA
GCCGCTTGCACACCTCCACGACCTGGATGTGTCCGACAACCAGCTGGAGCGAGTGCACCTG
TGATCCGAGGCCTCCGGGGCTGACGCCCTGCCGGCTGGCCGGCAACACCCGATTGCCAGC
TGCAGGCCCGAGGACCTGGCCGGCTGGCTGCCCTGCAGGAGCTGGATGTGAGCAACCTAACGCC
TGCAGGCCCTGCCTGGCGACCTCTCAGGCCCTTCCCCCGCTGCCCTGGCAGCTGCC
GCAACCCCTCAACTGCCGTGTGCCCTGAGCTGGTTGGCCCTGGTGCAGGAGAGCCACG
TCACACTGGCCAGCCCTGAGGAGACGCCCTGCCACTTCCGCCAAGAACGCTGGCCGGCTGC
TCCCTGGAGCTTGACTACGCCACTTGGCTGCCAGCCACCACACCAGCCACAGTGCCCA
CCACGAGGCCGTGGTGCAGGCCACAGCCTGTCTTAGCTGGCTCTACCTGGCTTA
GCCAACAGGCCGGCCACTGAGGCCAGGCCCTCCACTGCCCAACCGACTGTAGGGC
CTGTCCCCCAGCCCCAGGACTGCCAACCGTCCACCTGCCCTAATGGGGCACATGCCACCTGG
GGACACGGCACCACTGGCGTCTGTGCCCGAAGGCTTCACGGCCTGTACTGTGAGAGCC
AGATGGGGCAGGGGACACGCCAGGCCACACCAGTCACGCCGAGGCCACCAAGGTCCCTGA
CCCTGGGCATCGAGCCGGTGAGGCCACCTCCCTGCCGTGGGCTGCAGCGCTACCTCCAGG
GGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTATCGAACCTATGCCCTGATAAGC
GGCTGGTGACGCTGCCACTGCCCTGCCCTGAGTACACGGTACCCAGCTGCCGGCCA
ACGCCACTTACTCCGTCTGTCTGCCCTTGGGCCGGGGTGCCGGAGGGCGAGGAGG
CCTGCCGGGAGGCCATACACCCCAAGCCGTCCACTCCAACCACGCCCAAGTCACCCAGGCC
GCCAGGGCAACCTGCCCTCTCATGGCCCGCCCTGGCCGGTGTCCCTGCCGCCGTGG
CTGCCGTGGGGCAGCCTACTGTGTGCCGGGGGGGGCATGGCAGCAGGGCTCAGGACA
AAGGGCAGGTGGGGCAGGGCTGGGCCACTGGAACTGGAGGGAGTGAAGGTCCCTGGAGC
CAGGCCGAAGGCAACAGAGGGCGGTGGAGAGGCCCTGCCAGCGGGCTGAGTGTGAGGTGC
CACTCATGGCTTCCAGGGCCTGCCCTCAGTCACCCCTCCACGCCAAAGCCCAT**TAA**
CCAGAGAGAGACAGGGCAGCTGGGCCGGCTCTCAGCCAGTGAGATGCCAGCCCCCTCTG
CTGCCACACCACGTAAGTTCTCAGTCCCAACCTGCCGGATGTGTGCAGACAGGGCTGTGAC
CACAGCTGGCCCTGTTCCCTCTGCCACCTCGGTCTCCTCATCTGTGAGATGCTGTGCCAGC
TGACGAGCCCTAACGTCCCCAGAACCGAGTGCCTATGAGGACAGTGTCCGCCCTGCCCTCCGC
AACGTGCAGTCCCTGGCACGGCGGGCCCTGCCATGTGCTGTAACGCATGCCCTGGGCCCTGC
TGGGCTCTCCACTCCAGGCCACCTGGGGCCAGTGAAGGAAGCTCCGGAAAGAGCAGAG
GGAGAGCGGGTAGGGCGTGTGACTCTAGTCTTGCCGCCAGGAAGCGAAGGAACAAAGAA
ACTGGAAAGGAAGATGTTAGGAACATGTTTGCTTTTAAATATATATTTATAAGAG
ATCCTTCCCATTATTCTGGGAAGATGTTTCAAACTCAGAGACAAGGACTTTGGTTTG
TAAGACAAACGATGATGAAGGCCTTGTAAAGAAAAAATAAAGATGAAGTGTGAAA

16/168

FIGURE 16

MCSRVPLLPPLLLALGPGVQGCPSCQCSQPQTVFCTARQGTTVPRDVPPDTVGLYVFENG
ITMLDAGSFAGLPGLQLLDLSQNQIASLPSGVFQPLANLSNLDLTANRLHEITNETFRGLRRL
ERLYLGKNRIRHIQPGAFDTLDRLLELKLQDNELRALPPLRLPRLLLLDLSHNSLLALEPGIL
DTANVEALRLAGLGLQQLDEGLFSRLRNLDLDVSDNQLERVPPVIRGLRGLTRLRLAGNTRI
AQLRPEDLAGLAALQELDVSNLSQLPGDLSGLFPRLRLLAAARNPNCVCPLSWFGPWVRE
SHVTLASPEETRCHFPPKNAGRLLLELDYADFGCPATTTATVPTTRPVVREPTALSSSLAPT
WLSPTAPATEAPSPPSTAPPTVGPPQPPQDCPPSTCLNGGTCHLGTRHHLACLCPEGFTGLYC
ESQMGQGTRPSPTPVTPRPPRSLTGLIEPVSPSLRVGLQRYLQGSSVQLRSLRLTYRNLSGP
DKRLVTLRLPASLAETVTQLRPNATYSVCVMPPLGPGRVPEGEEACGEAHTPPAVHSNHAPVT
QAREGNLPLLIAPALAAVLLAALAAVGAAAYCVRRGRAMAAAQDKGQVGPAGPLELEGVKVP
LEPGPKATEGGGEALPSGSECEVPLMGFPGLQSPFHAKPYI

Important features:

Signal peptide:

amino acids 1-23

Transmembrane domain:

amino acids 579-599

EGF-like domain cysteine pattern signature.

amino acids 430-442

Leucine zipper pattern.

amino acids 197-219, 269-291

N-glycosylation sites.

amino acids 101-105, 117-121, 273-277, 500-504, 528-532

Tyrosine kinase phosphorylation sites.

amino acids 124-131, 337-345

N-myristoylation sites.

amino acids 23-29, 27-33, 70-76, 142-148, 187-193, 348-354,
594-600, 640-646

FIGURE 17

GCAGCGGCGAGGCGGGCGGTGGTGGCTGAGTCCGTGGCAGAGGCGAAGGCGACAGCTC**ATG**
CGGGTCCGGATAGGGCTGACGCTGCTGCTGTGCGGTGCTGAGCTTGGCCTCGGCGTCC
TCGGATGAAGAAGGCAGCCAGGATGAATCCTAGATTCCAAGACTACTTGACATCAGATGAG
TCAGTAAAGGACCATACTACTGCAGGCAGAGTAGTTGCTGGTCAAATATTCTTGATTGAGAA
GAATCTGAATTAGAATCCTCTATTCAAGAAGAGGAAGACAGCCTCAAGAGCCAAGAGGGGAA
AGTGTACAGAAGATATCAGCTTCTAGAGTCTCCAAATCCAGAAAACAAGGACTATGAAGAG
CCAAAGAAAGTACGGAAACCAGCTTGACCGCCATTGAAGGCACAGCACATGGGAGCCCTGC
CACTTCCCTTTCTTCTAGATAAGGAGTATGATGAATGTACATCAGATGGGAGGGAAAGAT
GGCAGACTGTGGTGTGCTACAACCTATGACTACAAAGCAGATGAAAAGTGGGCTTTGTGAA
ACTGAAGAAGAGGCTGCTAAGAGACGGCAGATGCAGGAAGCAGAAATGATGTATCAAACCTGGA
ATGAAAATCCTTAATGGAAGCAATAAGAAAAGCCAAAAAGAGAAGCATATCGGTATCTCCAA
AAGGCAGCAAGCATGAACCATAACCAAGCCCTGGAGAGAGTGTCATATGCTTTTATTG
GATTACTGCCACAGAATATCCAGGCAGCGAGAGAGATGTTGAGAAGCTGACTGAGGAAGGC
TCTCCAAGGGACAGACTGCTTGGCTTCTGTATGCCTCTGGACTTGGTGTAAATTCAAGT
CAGGCAAAGGCTTGTATATTACATTGGAGCTTGGGGCAATCTAATAGCCCACATG
GTTTGGTAAGTAGACTT**TAG**TTGGAGGCTAATAATATTAAACATCAGAAGAATTGTGGTTA
TAGCGGCCACAACCTTTCAGCTTCAGTCCAGATTGCTTGTATTAAGACCAATATTCA
GTTGAACCTCCTCAAATTCTGTTAATGGATATAACACATGGAATCTACATGAAATGAAAG
TTGGTGGAGTCCACAATTCTTAAAATGATTAGTTGGCTGATTGCCCTAAAAAGAGAG
ATCTGATAAAATGGCTTTAAATTCTGAGTTGGAATTGTCAGAATCATTTCACAT
TAGATTATCATAATTAAAAATTCTTCTGAAATTGTTCAAATTGTTAAATTGGTGGCTATA
GAAAAACACATGAAATATTACAAATTGGCAACAAATGCCCTAAGAATTGTTAAAATTCA
TGGAGTTATTGTGAGAATGACTCCAGAGAGCTACTTTCTGTTTACTTTCATGATT
GGCTGCTTCCATTATTCTGGTCATTATTGCTAGTGACACTGTGCCTGCTCCAGTAGTC
TCATTTCCTATTGCTAATTGTTACTTTCTTGCTAATTGGAAGATTAACTCATT
TTAATAAAATTATGTCTAAGATTAAAAA
AAA

FIGURE 18

MRVRIGLTLCAVLLSLASASSDEEGSQDESLDSTTTSDESVKDHTAGRVVAGQIFLDS
EESELESSIQEEEDSLKSQEGESVTEDISFLESPNPNENKDYEPPKKVRKPALTAIEGTAHGE
CHFPFLFLDKEYDECTS DGRDGRILWCATTYDYKADEKWGFCETEEEAAKRRQMQEAE
GMKILNGSNKKSQKREAYRYLQKAASMNHTKALERVSYALLFGDYLQPQNIQAAREMFEKL
GSPKGQTALGFLYASGLGVNSSQAKALVYYTFGALGGNLIAHMVLVSRL

Important features:

Signal peptide:

amino acids 1-21

N-glycosylation sites.

amino acids 195-199, 217-221, 272-276

Tyrosine kinase phosphorylation site.

amino acids 220-228

N-myristoylation sites.

amino acids 120-126, 253-259, 268-274, 270-274, 285-291, 289-295

Glycosaminoglycan attachment site.

amino acids 267-271

Microbodies C-terminal targeting signal.

amino acids 299-303

Type II fibronectin collagen-binding domain protein.

amino acids 127-169

Fructose-bisphosphate aldolase class-II protein.

amino acids 101-119

19/168

FIGURE 19

AATTACAGATTAAAGCCCATTCTGCAGTGGAAATTCTGAACTAGCAAGAGGACACCATCTTC
TTGTATTATAACAAGAAAGGAGTGTACCTATCACACACAGGGGGAAAAATGCTTTGGGTGC
TAGGCCTCCTAATCCTCTGGTTCTGTGGACTCGTAAAGGAAA~~ACTAAAGATTGAAGACA~~
TCACTGATAAGTACATTTCATCGTAAATCGCTGCCGTCTGACTGAATCAGGATCAACAGCCT
CTTTGATAAAAAGGGATTCATGTAATCGCTGCCGTCTGACTGAATCAGGATCAACAGCCT
TAAAGGCAGAAACCTCAGAGAGACTCGTACTGTGCTCTGGATGTGACCGACCCAGAGAATG
TCAAGAGGACTGCCAGTGGGTGAAGAACCAAGTTGGGAGAAAGGTCTCTGGGTCTGATCA
ATAATGCTGGTGTCCGGCGTGGCTCCCACACTGACTGGCTGACACTAGAGGACTACAGAG
AACCTATTGAAGTGAACCTGTTGGACTCATCAGTGTGACACTAAATATGCTCCCTTGGTCA
AGAAAGCTCAAGGGAGAGTTATTAAATGTCCTCAGTGGAGGTGCCTGCAATCGTTGGAG
GGGGCTATACTCCATCAAATATGCAGTGGAGGTTCAATGACAGCTTAAGACGGACATGA
AAGCTTTGGTGTGCACGTCTCATGCATTGAACCAGGATTGTTCAAAACAAACTGGCAGATC
CAGTAAAGGTATTGAAAAAAACTCGCCATTGGGAGCAGCTGTCCTCAGACATCAAACAAAC
AATATGGAGAAGGTTACATTGAAAAAAAGTCTAGACAAACTGAAAGGCAATAATCCTATGTGA
ACATGGACCTCTCCGGTGGTAGAGTGCATGGACCACGCTCTAACAAAGTCTCTCCCTAAGA
CTCATTATGCCGCTGGAAAAGATGCCAAATTTCTGGATACCTCTGTCTCACATGCCAGCAG
CTTGCAAGACTTTATTGTTGAAACAGAAAGCAGAGCTGGCTAATCCAAAGGCAGTGTGA
TCAGCTAACCAAAATGTCTCCCTCCAGGCTATGAAATTGGCGATTCAAGAACACATCTCCT
TTTCAACCCATTCTTATCTGCTCCAAACCTGGACTCATTAGATCGTGCTTATTGGATTGC
AAAAGGGAGTCCCACCCTCGTGGTGGTATCCAGGGTCCCTGCTCAAGTTCTTGAAAG
GAGGGCTGGAATGGTACATCACATAGGCAAGTCCCTGCCGTATTTAGGCTTGCTGCTTGG
TGTGATGTAAGGGAAATTGAAAGACTGCCATTCAAAATGATCTTACCGTGGCCTGCCCA
TGCTTATGGTCCCCAGCATTACAGTAACCTGTGAATGTTAAGTATCATCTTATCTAAATA
TTAAAAGATAAGTCACCCAAAAA~~AAAAAAAAAAAAAAAAAAAAAAAAAAAAA~~

20/168

FIGURE 20

MLFWVLGLLILCGFLWTRKGKLKIEDITDKYIFITGCDSGFGNLAARTFDKKGFHVIAACLTE
SGSTALKAETSERLRTVLLDVTDPENVKRTAQWVKNQVGEKGLWGLINNAGVPGVLAPTDWLT
LEDYREPIEVNLFGGLISVTLNMLPLVKKAQGRVINVSSVGGRLAIVGGGYTPSKYAVEGFNDS
LRRDMKAFGVHVSCIEPGLFKTNLADPVKVIEKKLAIWEQLSPDIKQQYGEGYIEKSLDKLKG
NKSYVNMDLSPVVECMDHALTSLFPKTHYAAAGKDAKIFWIPLSHMPAALQDFLLLKQKAELAN
PKAV

Important features of the protein:

Signal peptide:

amino acids 1-17

Transmembrane domain:

amino acids 136-152

N-glycosylation sites.

amino acids 161-163, 187-190 and 253-256

Glycosaminoglycan attachment site.

amino acids 39-42

N-myristoylation sites.

amino acids 36-41, 42-47, 108-113, 166-171, 198-203 and 207-212

21/168

FIGURE 21

CTGAGGCGGCGGTAGC**ATG**GAGGGGGAGAGTACGTCGGCGGTGCTCTCGGGCTTGTGCTCGG
CGCACTCGCTTCCAGCACCTAACACACGGACTCGGACACGGAAGGTTTCTTCTGGGAAGT
AAAAGGTGAAGCCAAGAACAGCATTACTGATTCCAAATGGATGATGTTGAAGTTGTTATAC
AATTGACATTCAAGAAATATATTCCATGCTATCAGCTTTAGCTTTATAATTCTCAGGCAG
AGTAAATGAGCAAGCACTGAAGAAAATATTATCAAATGTCAAAAAGAATGTGGTAGGTTGGTA
CAAATTCCGTCGTCAATTCAAGATCAGATCATGACGTTAGAGAGAGGCTGCTCACAAAAACTT
GCAGGAGCATTTCAAACCAAGACCTGTTCTGCTATTAAACACCAAGTATAAACAGA
AAGCTGCTCTACTCATCGACTGGAACATTCTTATATAAACCTCAAAAAGGACTTTTACAG
GGTACCTTAGTGGTTGCCAATCTGGCATGTCGAACAACACTGGTTATAAAACTGTATCAGG
TTCCTGTATGTCCACTGGTTAGCCGAGCAGTACAAACACACAGCTCTAAATTGGAGAAGA
AGATGGATCCTAAAGGAGGTACATAAGATAATGAAATGTATGCTTCATTACAAGAGGAATT
AAAGAGTATATGCAAAAAGTGGAAAGACAGTGAACAAGCAGTAGATAAAACTAGTAAAGGATGT
AAACAGATAAAACGAGAAATTGAGAAAAGGAGAGGAGCACAGATTCAAGGCAGCAAGAGAGAA
GAACATCCAAAAGACCCCTCAGGAGAACATTCTTCTTCAGGCATTACGGACCTTTTCC
AAATTCTGAATTCTTCATTCACTGTGTTATGTCTTAAAAAATAGACATGTTCTAAAGTAG
CTGTAACTACAACCACCATCTGATGTAGACAATCTGACCTTAATGGTAGAACACACTGA
CATTCTGAAGCTAGTCCAGCTAGTACACCACAAATCATTAAGCATAAAGCCTAGACTTAGA
TGACAGATGGCAATTCAAGAGATCTGGTTGTTAGATACACAAGACAAACGATCTAAAGCAA
TACTGGTAGTAGTAACCAAGATAAAGCATCCAAAATGAGCAGGCCAGAAACAGATGAAGAAAT
TGAAAAGATGAAGGGTTTGGTGAATATTCACTGGCTCCTACATT**TGAT**CTTTAACCTTA
CAAGGAGATTTTTATTGGCTGATGGTAAAGCCAAACATTCTATTGTTACTATGTT
GAGCTACTTGCAGTAAGTTCAATTGTTACTATGTTCACCTGTTGCAGTAATACACAGAT
AACTCTTAGTGCATTACTTCACAAAGTACTTTCAAACATCAGATGCTTTATTCCAAAC
CTTTTTCACCTTCACTAAGTTGAGGGGAAGGCTTACACAGACACATTCTTGAATT
GGAAAAGTGAGACCAGGCACAGTGGCTCACACCTGTAATCCAGCACTAGGAAAGACAAGTC
AGGAGGATTGATTGAAGCTAGGAGTTAGAGACCAGCCTGGCAACGTATTGAGACCATGTCTA
TTAAAAAAATGGAAAAGCAAGAATAGCCTTATTTCAAAATATGGAAAGAAATTATAT
GAAAATTATCTGAGTCATTAAATTCTCCTTAAGTGTACTTTAGAAGTACATTATGGC
TAGAGTTGCCAGATAAAATGCTGGATATCATGCAATAATTGCAAAACATCATCTAAAATT
AAAAAAAAAAAAAAAAAAAAAA

22/168

FIGURE 22

MEGESTSAVLSGFVLGALAFQHLNTDSDEGFLGEVKGEAKNSITDSQMDDVEVVTIDIQK
YIPCYQLFSFYNSGEVNEQALKKILSNVKKNVGWYKFRRHSDQIMTFRERLLHKNLQE^HF
NQDLVFLLLTPSIITESCSTHRLEHSLYKPQKGLFHRVPLVVANLGMSEQLGYKTVSGSCMST
GFSRAVQTHSSKFFEDGSLKEVHKINEMYASLQEELKSICKVEDSEQAVDKLVKDVNRLKR
EIEKRRGAQIQAAREKNIQKDPQENIFLCQALRTFFPNSEFLHSCVMSLKNRHVKSSCNYNH
HLDVVDNLTLTLMVEHTDIPPEASPASTPQIIKHKA
LDLDDRWFKRSRLLDTQDKRSKANTGSSN
QDKASKMSSPETDEEIEKMKGFGEYSRSPTF

Important features:

Signal peptide:

amino acids 1-19

N-glycosylation sites.

amino acids 75-79, 322-326

N-myristoylation site.

amino acids 184-154

Growth factor and cytokines receptors family.

amino acids 134-150

23/168

FIGURE 23

GGCACAGCCGCGCGGGAGGGCAGAGTCAGCCGAGCCGAGTCAGCCGGACGAGCGGACCAGCGCAGGGCAGCC
CAAGCAGCGCGCAGCGAACGCCGCCGCCACACCCCTCTCGGGTCCCCGGCGCCTGCCACCCCTCC
TTCCCGCGTCCCCGCCCTGCCGCCAGTCAGCTTGGCGGGTCGCTGCCCGCGAAACCCCGAGGTACCCAGCC
CGCGCCTCTGCTTCCCTGGGCCGCCCTCCACGCCCTCCTCTCCCTGGCCCGCCTGGCACCGGG
ACCGTTGCCTGACCGAGGCCAGCTACTTTGCCCGCTCCTCCGCCTGCTGCCCTTTCCACCAACT
CCAACCTCTCCCTCCAGCTCCACTCGCTAGTCCCCGACTCCGCCAGCCCTGGCCCGCTGCCGTAGGCCGC
TTCCCGTCCGGTCCCAAAGGTGGAACCGCGTCCGCCCGGCCGACCATGGCACGGTTGGCTTGGCGCTT
CTCTGCACCCCTGGCAGTGCTCAGCGCCGCGCTGGCTGCCGAGCTCAAGTCAAAAGTTGCTCGGAAGTGC
CGTCTTACGTGTCAAAGGCTTCAACAAGAACGATGCCCTCCACGAGATCAACGGTGATCATTGAAGATC
TGTCCCCAGGGTTCTACCTGCTGCTCTCAAGAGATGGAGGAGAAGTACAGCCTGCAAAGTAAAGATGATTCAA
AGTGTGGTCAGCGAACAGTCAATCATTGCAAGCTGTCTTCACGTTACAAGAACGATTTGATGAATTCTC
AAAGAACTACTTGAAAATGCAGAGAAATCCCTGAATGATATGTTGTGAAGACATATGCCATTACATGCAA
AATTCTGAGCTATTAAAGATCTTCGTAGAGTTACTACGTGGTGGAAATGTGAACCTGGAAGAA
ATGCTAAATGACTCTGGCTGCCCTGGAGCGGATGTTCCGCTGGTGAACCTCCAGTACCAACTTACAGAT
GAGTATCTGGAATGTGAGCAAGTATACGGAGCAGCTGAAGCCCTCGGAGATGTCCTCGCAAATTGAAGCTC
CAGGTTACTCGTGTCTTGAGCAGCCGTACTTCGCTCAAGGCTTAGCGGTTGCCGGAGATGTCGTGAGCAAG
GTCTCCGTGGTAAACCCACAGCCCAGTGTACCCATGCCCTGTGAAGATGATCTACTGCTCCACTGCCGGGGT
CTCGTACTGTGAAGCCATGTTACAACATACTGCTCAAACATCATGAGAGGCTGTTGCCAACCAAGGGATCTC
GATTTGAATGGAACAATTCTAGATGCTATGCTGATGGTGGCAGAGAGGCTAGAGGGCTTCAACATTGAA
TCGGTCATGGATCCCCTCGATGTGAAGATTCTGATGCTATTATGAACATGCAGGATAATAGTGTCAAGTGTCT
CAGAAGGTTTCCAGGGATGTGGACCCCCCAAGCCCTCCAGCTGGACGAATTCTCGTTCCATCTGAAAGT
GCCCTCAGTGTGCTTCAGACCAACATCCCCGAGGAACGCCAACACAGCAGCTGGCACTAGTTGGACCGA
CTGGTTACTGATGTCAGGAGAAACTGAAACAGGCCAAGAAATTCTGGTCCTCCCTCCGAGCAACGTTGCAAC
GATGAGAGGATGGCTGCAGGAAACGGCAATGAGGATGACTGTTGAATGGAAAGGAAAAGCAGGTACCTGTT
GCAGTGACAGGAAATGGATTAGCCAACCAGGGCAACAACCCAGAGGTCCAGGTTGACACCAGCAAACAGACATA
CTGATCCTCGTCAAATCATGGCTTCTCGAGTGATGACCAGCAAGATGAAGAATGCATAACATGGAACGACGTG
GACTTCTTGATATCAGTGATGAAAGTAGTGGAGAAGGAAGTGGAAAGTGGCTGTGAGTATCAGCAGTGCCCTCA
GAGTTTGACTACAATGCCACTGACCATGCTGGGAAGAGTGCCAATGAGAAAGCCGACAGTGCTGGTGTCCGT
GGGGCACAGGCCTACCTCCTCACTGTCTTCGATCTTGTGGTTATGCAGAGAGAGTGGAGATAATTCTCA
AACTCTGAGAAAAAGTGTTCATCAAAAGTTAAAGGCACCAGTTACCTTCTACCATCCTAGTGACTTGC
TTTTAAATGAATGGACAACAATGTACAGTTTACTATGTGGCCACTGGTTAAGAAGTGCTGACTTGT
TCATTCACTTGGAGGAAAGGGACTGTGCATTGAGTTGGTCTGCTCCCCAAACCATGTTAACGTGGCT
AACAGTGAGGTACAGAACTATAGTTAGTGTGCATTGTGATTTTACACTCTATTATTTGTTGATGTT
TTCTCATTCTGTTGGGTTTTTCAACTGTGATCTGCCCTGTTCTTACAAGCAAACCAGGGTCC
CTTGGCACGTAACATGTACGTATTCTGAAATATTAAATAGCTGTACAGAACGAGGTTATTATCATGTTATC
TTATTAAAAAGAAAAAGCCAAAAAGC

24/168

FIGURE 24

MARFGLPALLCTLAVLSAALLAAELKSKCSEVRRLYVSKGFNKNDAPLHEINGDHLKICPQG
STCCSQEMEEKYSLQSKDDFKSVVSEQCNHLQAVFASRYKKFDEFFKELLENAEKSLSNDMFVK
TYGHLYMQNSELFKDLFVELKRYYVVGVNLEEMLNDFWARLLERMFRVLVNSQYHFTDEYLEC
VSKYTEQLKPFGDVPRKLKLQVTRAFVAARTFAQGLAVAGDVSKVSVNPTAQCTHALLKMI
YCSHCRGLVTVKPCNYCSNIMRGCLANQGDLDFEWNNFIDAMLMVAERLEGPFNIESVMDPI
DVKISDAIMNMQDNSVQVSQKVFGCGPPKPLPAGRISRSISESAFSARFRPHHPEERPTAA
GTSLDRLVTDVKEKLQAKFWSSLPSNVCNDERMAAGNGNEDDCWNGKGKSRYLFAVTGNGL
ANQGNPPEVQVDTSKPDILILRQIMALRVMTSKMKNAYNGNDVDFDISDESSGEGSGSGCEY
QQCPSEFDYNATDHAGKSANEKADSAGVRPGAQAYLLTVFCILFLVMQREWR

Important features:

Signal peptide:

amino acids 1-22

ATP/GTP-binding site motif A (P-loop) .

amino acids 515-524

N-glycosylation site.

amino acids 514-518

Glycosaminoglycan attachment sites.

amino acids 494-498, 498-502

N-myristoylation sites.

amino acids 63-69, 224-230, 276-282, 438-444, 497-503, 531-537

Glypicans proteins.

amino acids 54-75, 105-157, 238-280, 309-346, 423-460, 468-506

25/168

FIGURE 25

CTCGCCCTCAAATGGGAACGCTGGCCTGGGACTAAAGCATAGACCACCAGGCTGAGTATCCTG
ACCTGAGTCATCCCCAGGGATCAGGAGCCTCCAGCAGGGAACCTCCATTATATTCTTCAAGC
AACTTACAGCTGCACCGACAGTTGCGATGAAAGTTCTAATCTCTCCCTCCTGTTGCTGC
CACTAATGCTGATGTCCATGGTCTCTAGCAGCCTGAATCCAGGGTCGCCAGAGGCCACAGGG
ACCGAGGCCAGGCTCTAGGAGATGGCTCCAGGAAGGCAGGCCAAGAATGTGAGTGCAAAGATT
GGTTCCCTGAGAGCCCCGAGAAGAAAATTCATGACAGTGTCTGGGCTGCCAAAGAACAGCAGTGC
CCTGTGATCATTCAAGGGCAATGTGAAGAAAACAAGACACCAAAGGCACCACAGAAAGCCAA
ACAAGCATTCCAGAGCCTGCCAGCAATTCTCAAACAATGTCAGCTAAGAACGCTTGTCTGC
CTTGTAGGAGCTCTGAGCGCCCACCTCTCCAATTAAACATTCTCAGCCAAGAACAGTGAG
CACACCTACCAGACACTCTCTCCCACCTCACTCTCCACTGTACCCACCCCTAAATCAT
TCCAGTGCTCTCAAAAAGCATGTTTCAAGATCATTGTTGCTCTCTAGTGTCTT
CTTCTCTCGTCAGTCTAGCCTGTGCCCTCCCTACCCAGGCTTAGGCTTAATTACCTGAAA
GATTCCAGGAAACTGTAGCTCCTAGCTAGTGTCAATTAAACCTTAAATGCAATCAGGAAAGTA
GCAAACAGAAGTCATAAAATATTTAAATGTCAAAAAAAAAAAAAAA

26/168

FIGURE 26

MKVLISLLLLPLMLMSMVSSLNPGVARGHRDRGQASRRWLQEGGQECECKDWFLRAPRRK
FMTVSGLPKKQCPCDHFKGKVNKKTRHQRHHRKPNKHSRACQQFLKQCQLRSFALPL

Important features:

Signal peptide:

amino acids 1-22

N-myristoylation sites.

amino acids 27-33, 46-52

27/168

FIGURE 27

GGACGCCAGCGCCTGCAGAGGCTGAGCAGGGAAAAAGCCAGTGCCTCAGCGGAAGCACAGCTC
AGAGCTGGTCTGCCATGGACATCCTGGTCCACTCCTGCAGCTGCTGGTCTGCTTCTACCC
TGCCCCTGCACCTCATGGCTCTGCTGGCTGCTGGCAGCCCCTGTGCAAAAGCTACTTCCCCT
ACCTGATGCCGTGCTGACTCCAAAGAGCAACCGCAAGATGGAGAGCAAGAACGGGAGCTCT
TCAGCCAGATAAAGGGGCTTACAGGAGCCTCCGGAAAGTGGCCCTACTGGAGCTGGCTGCG
GAACCGGAGCCAACTTCAGTTCTACCCACCGGGCTGCAGGGTCACCTGCCTAGACCCAAATC
CCCACTTGAGAAGTTCTGACAAAGAGCATGGCTGAGAACAGGCACCTCCAATATGAGCGGT
TTGTGGTGGCTCCTGGAGAGGACATGAGACAGCTGGCTGATGGCTCCATGGATGTGGTGGTCT
GCACTCTGGTGTGCTGTGCTCTGAGAGCCCAGGAAGGTCTGCAGGGAGGTCCGGAGAGTAC
TGAGACCAGGGAGGTGTGCTCTTCTGGAGACATGGCAGAACCATATGGAGCTGGCCT
TCATGTGGCAGCAAGTTTGAGCCCACCTGGAAACACATTGGGATGGCTGCTGCCTCACCA
GAGAGACCTGGAAGGATCTTGAGAACGCCAGTTCTCCGAAATCCAATGGAACGACAGCCCC
CTCCCTGAAGTGGCTACCTGTTGGCCCCACATCATGGAAAGGCTGTCAAACAATCTTCC
CAAGCTCCAAGGCACTCATTGCTCTCCCCAGCCTCCAATTAGAACAGCCACCCACCAGC
CTATCTATCTTCACTGAGAGGGACTAGCAGAATGAGAGAACATTGATGTACCACTACT
AGTCCCTCTCTCCCCAACCTCTGCCAGGGCAATCTCAACTTCAATCCGCCTCGACAGTGA
AAAAGCTCTACTTCTACGCTGACCCAGGGAGGAAACACTAGGACCCCTGTTGTATCCTCAA
CAAGTTCTGGACTAGTCTCCAACGTTGCCTCCAATGTTGTCCTTCCTCGTTCCCAT
GGTAAAGCTCCTCTCGCTTCTCCTGAGGCTACACCCATGCGTCTCTAGGAACCTGGTCACAA
AAGTCATGGTGCCTGCATCCCTGCCAACGCCCTGACCCCTCTCCCCACTACCACCTCTT
CCTGAGCTGGGGCACCAGGGAGAACATCAGAGATGCTGGGATGCCAGAGCAAGACTCAAAGAG
GCAGAGGTTTGTCTCAAATATTTTAATAAATAGACGAAACCACG

28/168

FIGURE 28

MDILVPLLQLLVLLTLPLHLMALLGCWQPLCKSYFPYLMAVLTPKSNRKMESKKRELFSQIK
GLTGASGKVALLELGCCTGANFQFYPPGCRVTCLDPNPHFEKFLTKSMAENRHLQYERFVVAP
GEDMRQLADGSMDVVVCTLVLCVQSPRKVLQEVRRVLRPGGVLFWEHVAEPYGSWAFMWQQ
VFEPTWKHIGDGCCLTRETWKDLENAQFSEIQMERQPPPLKWLPVGPHIMGKAVKQSFPSKAL
LICSFPSLQLEQATHQPIYLPLRGT

Important features:

Signal peptide:

amino acids 1-23

Leucine zipper pattern.

amino acids 10-32

N-myristoylation sites.

amino acids 64-70, 78-84, 80-86, 91-97, 201-207

29/168

FIGURE 29

CAATTTGCCTATCCACCTCCCCAAGCCCCCTTACCTATGCTGCTGCTAACGCTGCTGCTG
CTGCTGCTGCTGCTTAAAGGCTCATGCTTGGAGTGGGGACTGGTCGGTCCCCAGAAAGTCTCT
TCTGCCACTGACGCCCATCAGGGATTGGGCCTTCTTCCCCCTCCTTCTGTGTCTCCTG
CCTCATCGGCCTGCCATGACCTGCAGCCAAGCCCAGCCCCGTGGGAAGGGGAGAAAGTGGGG
GATGGCTAAGAAAGCTGGGAGATAGGAAACAGAAGAGGGTAGTGGGTGGCTAGGGGGCTGC
CTTATTAAAGTGGTTGTTATGATTCTTACTAATTATAACAAAGATATTAAGGCCCTGTT
CATTAAGAAATTGTTCCCTCCCTGTGTTCAATGTTGTAAGATTGTTCTGTGTAAATATG
TCTTTATAATAACAGTTAAAGCTGAAAAAAAAAAAAAAA

30/168

FIGURE 30

MLLLTL₁₁LLKGS₁₄CLEWGLVGAQKVSSATDAPIRDWAFFPPSFLCLLPHRPAMTC₂₀SQAQP
RGEGEKVGDG

Important features:

Signal peptide:

amino acids 1-15

Growth factor and cytokines receptors family:

amino acids 3-18

31/168

FIGURE 31

GTTCGAATTCTTCAACTATACCCACAGTCCAAAAGCAGACTCACTGTGTCCCAGGCTACCAG
TTCCTCCAAGCAAGTCATTTCCCTATTTAACCGATGTGTCCCTCAAACACCTGAGTGCTACT
CCCTATTTGCATCTGTTGATAATGATGTTGACACCCCTCCACCGAATTCTAAGTGGAAATCA
TGTCGGGAAGAGATACAATCCTGGCCTGTGTATCCTCGCATTAGCCTGTCTTGGCCATGA
TGTTTACCTTCAGATTCATCACCAACCCCTCTGGTTCACATTTCATTCATTGGTTATTTGG
GATTGTTGTTGTCTCGGGTGTATGGTGGCTGTATTATGACTATACCAACGACCTCAGCA
TAGAATTGGACACAGAAAGGGAAAATATGAAGTGCCTGCTGGGTTGCTATCGTATCCACAG
GCATCACGGCAGTGCCTCGTCTGATTTGTTCTCAGAAAGAGAATAAAATTGACAGTTG
AGCTTTCCAAATCACAAATAAAGCCATCAGCAGTGCTCCCTCCTGCTGTTCCAGCCACTGT
GGACATTTGCCATCCTCATTCTGGGCTCTGGGTGGCTGTGCTGCTGAGCCTGGGAA
CTGCAGGAGCTGCCAGGTTATGGAAGGCGCCAAGTGGAAATATAAGCCCCTTCGGGCATTC
GGTACATGTGGTCGTACCATTAATTGGCCTCATCTGGACTAGTGAATTCATCCTGCGTGCC
AGCAAATGACTATAGCTGGGCAGTGGTTACTTGTATTTCAACAGAAGTAAAAATGATCCTC
CTGATCATCCCATCCTTCGTCTCTCCATTCTTCTTCTACCATCAAGGAACCGTTGTGA
AAGGGTCATTTAATCTCTGTTGAGGATTCCGAGAATCATTGTCATGTACATGCAAAACG
CACTGAAAGAACAGCAGCATGGTGCATTGTCCAGGTACCTGTTCCGATGCTGCTACTGCTGTT
TCTGGTGTCTTGACAAATACCTGCTCCATCTCAACCAGAATGCATATACTACAACGTCTATT
ATGGGACAGATTCTGTACATCAGAAAAGATGCATTCAAAATCTGTCCAAGAACTCAAGTC
ACTTTACATCTATTAACGTCTTGGAGACTTCATAATTTCTAGGAAAGGTGTTAGTGGTGT
GTTCACTGTTGGAGGACTCATGGCTTTAATCACAATCGGGCATTCCAGGTGTGGCAG
TCCCTCTGTTATTGGTAGCTTTTGCTACTTAGCTAGCCATAGTTTATCTGTGTTG
AAACTGTGCTGGATGCACCTTCCTGTGTTGCTGTTGATCTGAAACAAATGATGGATCGT
CAGAAAAGCCCTACTTATGGATCAAGAATTCTGAGTTCGAAAAAGGAGCAACAAATTAA
ACAATGCAAGGGCACAGCAGGACAAGCACTCATTAAGGAATGAGGAGGGAACAGAACTCCAGG
CCATTGTGAGA**TAG**ATACCCATTTAGGTATCTGTACCTGGAAAACATTCTTAAGAGCCA
TTTACAGAATAGAAGATGAGACCACTAGAGAAAAGTTAGTGAATTTTTAAAAGACCTAA
TAAACCCTATTCTCCTCAAAA

32/168

FIGURE 32

MSGRTILGLCILALALSLAMMFTFRFITTLLVHIFISLVLGLLFVCGVLWWLYDYTNDSL
IELDTERENMKCVLGFAIVSTGITAVLLVLIFVLRKRIKLTVELFQITNKAISAPFLLFQPL
WTFAILIFFWVLWVAVLLSLGTAGAAQVMEGGQVEYKPLSGIRYMWSYHLIGLIWTSEFILAC
QQMTIAGAVVTCYFNRSKNDPPDHPILSSLSILFFYHQGTVVKGSFLISVVRIPRIIVMYMQN
ALKEQQHGALSRYLFRCCYCCFWCLDKYLLHLNQNAYTTAINGTDFCTSAKDAFKILSKNSS
HFTSINCQDFIIIFLGKVLVVCFTVFGGLMAFNYNRAFQVWAVPLLLVAFFAYLVAHSFLSVF
ETVLDALFLCAVDLETNDGSSEKPYFMDQEFLSFVKRSNKLNNARAQQDKHSLRNEEGTELQ
AIVR

Important features:

Signal peptide:

amino acids 1-20

Putative transmembrane domains:

amino acids 35-54, 75-97, 126-146, 185-204, 333-350, 352-371

N-glycosylation sites.

amino acids 204-208, 295-299, 313-317

N-myristoylation sites.

amino acids 147-153, 178-184, 196-202, 296-275, 342-348

FIGURE 33

GTTCGATTAGCTCCTCTGAGAAGAAGAGAAAAGGTTCTGGACCTCTCCCTGTTCTTCTCTTGA
GAATAATTGTATGGGATTTGTGATGCAGGAAAGCTAAGGGAAAAAGAATATTCTATTCTGTG
TGGTGAAAATTGGGAAAGGGAAAGGGAAAGGGAAAGGGTGTGATTCTGTTCTGTTCTGTTCTG
GAGGACTGTTGTTCTCACTATGAAGGCATCTGTATTGAAATGTTCTGTTCTGTTCTGTTCTG
TGGAGTACATTCAAACAAAGAAACGGCAAAGAAGATTAAAAGGCCAAGTTCACTGTGCCTCA
GATCAACTGCGATGTCAAAGCCGGAAAGATCATCGATCCTGAGTTCATGTTGAAATGTCAGC
AGGATGCCAAGACCCAAATACCATGTTATGGCACTGACGTGATGCATCCTACTCCAGTGT
GTGTGGCGCTGCCGTACACAGTGGTGTGCTTGATAATTCAAGGAGGGAAATACTTGTTCGGAA
GGTTGCTGGACAGTCTGGTTACAAAGGGAGTTATTCCAACGGTGTCCAATGTTATCCCTACC
ACGATGGAGAGAATCCTTATCGTCTAGAAAGTAAACCCAAAAGGGTGTAAACCTACCCATC
AGCTCTTACATACTCATCGAAAAGTCCAGCTGCCAAGCAGGTGAGACCACAAAAGCCTA
TCAGAGGCCACCTATTCCAGGGACAACGTGACAGCCGGTCACTCTGATGCAGCTTCTGGCTGT
CACTGTAGCTGTGCCACCCCCACCACCTGCCAAGGCCATCCCTCTGCTGTTCTACCCAC
CAGCATCCCCAGACCACAATCAGTGGCCACAGGAGCCAGGAGATGGATCTGGTCCACTGC
CACCTACACAAGCAGCAAAACAGGCCAGAGCTGATCCAGGTATCAAAGGCAAGATCCTC
AGGAGCTGCCTCCAGAAACCTGTTGGAGCGGATGTCAGCCTGGACTTGTCCAAAAGAAGA
ATTGAGCACACAGTCTTGGAGCCAGTATCCCTGGAGATCCAAACTGCAAAATTGACTTGTC
GTTTTAATTGATGGGAGCACCAGCATGGCAAACGGGATTCCAATCAGAACAGCAGCTCCT
GGCTGATGTTGCCAAGCTCTTGACATTGGCCCTGCCGGTCACTGATGGTGTGTTCCAGTA
TGGAGACAACCTGCTACTCACTTAAACCTCAAGACACACACGAATTCTGAGATCTGAAGAC
AGCCATAGAGAAAATTACTCAGAGAGGAGACTTCTATGTAGGTGGCCATCTCCTTGT
GACCAAGAACTTCTTCCAAAGCCAATGGAAACAGAACGGGGCTCCAAATGTGGTGGTGGT
GATGGTGGATGGCTGCCACGGACAAAGTGGAGGGAGGCTCAAGACTTGCAGAGAGTCAGG
AATCAACATTCTCATCACCATTGAAGGTGCTGCTGAAATGAGAACAGTATGTGGTGG
GCCCAACTTGCAAACAGGCCGTGTCAGAACAAACGGCTCTACTCGCTCCACGTGCAGAG
CTGGTTTGGCCTCCACAAGACCCCTGCAAGCCTCTGGTGAAGCGGGTCTGCGACACTGACCGCCT
GGCCTGCAAGACCTGCTTGAACCTGGCTGACATTGGCTCGTCATCGACGGCTCCAGCAG
TGTGGGGACGGCAACTTCCGCACCGTCTCCAGTTGTGACCAACCTCACCAAAAGAGTTGA
GATTTCCGACACGGACACCGCATCGGCATCGGGGCCGTGCAGTACACCTACGAACAGCGGGCTGGAGTT
TGGGTTGACAAGTACAGCAGCAAGCCTGACATCCTCAACGCCATCAAGAGGGTGGCTACTG
GAGTGGTGGCACCAGCACGGGGCTGCCATCAACTTCCGCTGGAGCAGCTTCAAGAACAGTC
CAAGCCCAACAAAGAGGAAGTTAATGATCCTCATCACCGACGGAGGTCTACGACGACGTCCG
GATCCCAGCCATGGCTGCCATCTGAAGGGAGTGTACACCTATGCGATAGGCCTGGCTGGC
TGCCCAAGAGGAGCTAGAAGTCATTGCCACTCACCCGCCAGAGACCACCTCTTCTTGTGGA
CGAGTTGACAACCTCATCAGTATGTCCCCAGGATCATCAGAACATTGTACAGAGTTCAA
CTCACAGCCTCGGAACTGATTCAAGAGCAGGCAGAGCACCAAGTGTGCTTACTAAGT
ACGTGTTGGACCACCCACCGCTTAATGGGGCACGCACGGTGCATCAAGTCTGGCAGGGCA
TGGAGAAACAAATGTCTTGTATTATTCTTGCATCATGCTTTCATATTCCAAAAGTGG
AGTTACAAAGATGATCACAAACGTATAGAATGAGCCAAAGGCTACATCATGTTGAGGGTGT
GGAGATTTACATTGACAATTGTTCAAAATAATGTTCGGAATACAGTGCAGCCCTTAC
GACAGGCTTACGTAGAGCTTGTGAGATTAAAGTTGTTATTCTGATTGAACCTGTAA
CCCTCAGCAAGTTCATTTGTGATGACAATGTAGGAATTGCTGAAATTAAAGTTAGAAGG
ATGAAAAAATAAG
AAG

FIGURE 34

MRTVVLTMKASVIEMFLVLLVTGVHSNKETAKKIKRPKFTVPQINCDVKAGKIIDPEFIVKCP
AGCQDPKYHVYGTDVYASYSSVCGAAVHSGVLDNSGGKILVRKVAGQSGYKGSYSNGVQSLSL
PRWRESFIVLESKPKKGVTPSALTYSSSKSPAAQAGETTKAYQRPIP GTTAQPVTLQMQLLA
VTAVATPTTLPRPSPSAASTTSIPRPQSVGHRSQEMDLWSTATYTSSQRPRADPGIQRQDP
SGAAFQKPGADVSLGLVPKEELSTQSLEPVSLGDPNCKIDLSFLIDGSTSIGKRRFRIQKQL
LADVAQALDIGPAGPLMGVVQYGDNPATHFNLKTHNSRDLKTAIEKITQRGGLSNVGRAISF
VTKNFFSKANGNRSGAPVVVMVDGWPDKVEEASRLARESGINIFFITIEGAAENEKQYVV
EPNFANKAVCRTNGFYSLHVQSWFGLHKTQPLVKRVCDTDRLLACSKTCLNSADIGFVIDGSS
SVGTGNFRTVLQFVTNLTKFEISDTDTRIGAVQYTYEQRLEFGFDKYSSKPDILNAIKRVGY
WSGGTSTGAAINFQLEQLFKSKPNKRKLMILITDGRSYDDVRI PAMAAHLKGVITYAIGVAW
AAQEELEVIATHPARDHSFFVDEFDNLHQYVPRIIQNICTEFNSQPRN

Important features:

Signal peptide:

amino acids 1-26

Transmembrane domain:

amino acids 181-200

N-glycosylation sites.

amino acids 390-394, 520-524

N-myristoylation sites.

amino acids 23-29, 93-99, 115-121, 262-268, 367-373, 389-395,
431-437, 466-472, 509-515, 570-576, 571-577, 575-581, 627-633

Amidation site.

amino acids 304-308

FIGURE 35

CCGAGCACAGGAGATTGCCTGCGTTAGGAGGTGGCTGCGTGTGGAAAAGCTATCAAGGAA
GAAATTGCCAACCATGTCTTTCTGTTTCAGAGTAGTCACAACAGATCTGAGTGT
TAATTAAGCATGGAATACAGAAAACAACAAAAACTTAAGCTTAATTCATCTGGAATTCCA
CAGTTTCTTAGCTCCCTGGACCCGGTTGACCTGTTGGCTCTCCCGCTGGCTGCTATCAC
GTGGTGCTCTCCGACTACTCACCCCCGAGTGTAAAGAACCTTCGGCTCGCGTGCCTGAGCTG
CTGTGGATGGCCTCGGCTCTGGACTGTCCTCCGAGTAGGATGTCAGTGAGATCCCTAAA
TGGAGCCTCCTGCTGTCACTCCTGAGTTCTTGTGATGTGGTACCTCAGCCTCCCCAC
TACAATGTGATAGAACCGCGTGAACGGATGTACTTCTATGAGTATGAGCCGATTACAGACAA
GACTTTCACTTCACACTCGAGAGCATTCAAACACTGCTCTCATCAAAATCCATTCTGGTCATT
CTGGTGACCTCCCACCCCTCAGATGTGAAAGCCAGGCAGGCCATTAGAGTTACTGGGTGAA
AAAAAGTCTTGGTGGGATATGAGGTTCTTACATTTCTTATTAGGCCAAGAGGCTGAAAAG
GAAGACAAAATGTTGGCATTGTCCTTAGAGGATGAAACACCTCTTATGGTACATAATCCGA
CAAGATTTTAGACACATATAATAACCTGACCTTGAAAACCATTATGGCATTCAAGGTGGTA
ACTGAGTTTGCCCCAATGCCAAGTACGTAATGAAGACAGACACTGATGTTTCATCAATACT
GGCAATTAGTGAAGTATCTTAAACCTAAACCACACTCAGAGAAGTTTACAGGTTATCCT
CTAATTGATAATTATTCTATAGAGGATTTACCAAAAAACCCATTTCCTTACAGGAGTAT
CCTTCAAGGTGTTCCCTCCACTGCACTGGGTTGGGTTATATAATGTCCAGAGATTGGTG
CCAAGGATCTATGAAATGATGGTCACGTAAAACCCATCAAGTTGAAGATGTTATGTCGGG
ATCTGTTGAATTATTAAAAGTGAACATTCAATTCCAGAACACACAAATCTTCTTCTA
TATAGAATCCATTGGATGTCGTCAACTGAGACGTGTGATTGCAGCCATTGGCTTTCTTCC
AAGGAGATCATCACTTTGGCAGGTCATGCTAAGGAACACACATGCCATTTAACTTCAC
ATTCTACAAAAAGCCTAGAAGGACAGGACACCTTGTGGAAAGTGTAAATAAGTAGGTACTG
TGGAAAATTCACTGGGAGGTACACTTGTGATTATTAGTCAGGCCCTCAAAGATGATATGTGG
AGGAATTAAATATAAGGAATTGGAGGTTTGCTAAAGAAATTATAGGACCAACAAATTG
GACATGTCATTCTGTAGACTAGAATTCTTAAAGGGTGTACTGAGTTATAAGCTCACTAGG
CTGTAAAAACAAAACAATGTAGAGTTTATTGAACAAATGTAGTCAGTCACTTGAAGGTT
GTATATCTTATGTGGATTACCAATTAAAAATATGTAGTTCTGTGTCAAAAACTTCTTCA
CTGAAGTTACTGAACAAAATTACCTGTTGGTCATTATAAAGTACTTCAAGATGTT
GCAGTATTTCACAGTTATTATTAAAATTACTTCAACTTGTGTTAAATGTTTGAC
GATTCAATACAAGATAAAAAGGATAGTGAATCATTCTTACATGCAAACATTCCAGTTAC
TTAACTGATCAGTTATTATTGATACATCACTCCATTAAATGTAAAGTCATAGGTCAATTG
ATATCAGTAATCTCTGGACTTGTAAATATTTACTGTGGTAATATAGAGAAGAATTAAAG
CAAGAAAATCTGAAAA

FIGURE 36

MASALWTVLPSRMSLRSLKWSLLLLSLLSFFVMWYLSLPHYNVIERVNWMYFYEYEPIYRQDF
HFTLREHSNC SHQNPFLVILVTSHPSDVKARQAIRVTWGEKKSWWGYEVLTFFLLGQEAEKED
KMLALSLEDEHLLYGDIIRQDFLDTYNNLTLKTIMAFRWVTEFCPNAKYVMKTDTDVFINTGN
LVKYLLNLNHSEKFFTGYPLIDNYSYRGFYQKTHISYQEYPKVFPPYCSGLGYIMSRDLVPR
IYEMMGHVKPIKFEDVYVGICLNLLKVNIHIPEDTNLFFLYRIHLDVCQLRRVIAAHGFSSKE
IITFWQVMLRNTTCHY

Important features:

Type II transmembrane domain:

amino acids 20-39

N-glycosylation sites.

amino acids 72-76, 154-158, 198-202, 212-216, 326-330

Glycosaminoglycan attachment site.

amino acids 239-243

Ly-6 / u-PAR domain proteins.

amino acids 23-37

N-myristoylation site.

amino acids 271-277

FIGURE 37

CGCTCGGGCACCGCGCGCAAGGATGGAGCTGGTTGCTGGACGCGAGTGGGCTCACTTTCTTCAGCTCCT
TCTCATCTCGCCTTGCCAAGAGAGTACACAGTCATTAATGAAGCCTGCCCTGGAGCAGAGTGGAAATATCATGTG
TCGGGAGTGTGAATATGATCAGATTGAGTGGCTGCCCTGGAGCAGAGTGGAAAGAGGGAGTCGTGGGTTATACCATCCC
TTGCTGCAGGAATGAGGAGAATGAGTGTGACTCCTGCCTGATCCACCCAGGTTGACCATCTTGAAAAGTGCAGAGTGGCG
GAGCTGCCGAAATGGCTCATGGGGGGTACCTGGATGACTTCTATGTGAAGGGGTTCTACTGTGAGCAGATTTGTTGGA
AGCAGGCTGGTACGGAGGAGACTGCATGCGATGTGCCAGGTTCTGCGAGCCCCAAAGGGTCAGATTTGTTGGA
AAGCTATCCCCTAAATGCTCACTGTGAATGGACCATTGCTAAACCTGGGTTGTCATCCAACTAAGATTGT
CATGTTGAGTCTGGAGTTGACTACATGTGCCAGTATGACTATGTTGAGGTTCGTGATGGAGACAAACCGCGATGG
CCAGATCATCAAGCGTGTGTCAGGCAACGAGCGGCCAGCTCTATCCAGAGCATAGGATCCTCACTCCACGTCCT
CTTCCACTCCGATGGCTCCAAGAATTGACGGTTCCATGCCATTATGAGGAGATCACAGCATGCTCCTCATC
CCCTTGTTCATGACGGCACGTGCGCCTTGACAAGGCTGGATCTTACAAGTGTGCCCTGCTGGCAGGCTATAC
TGGCAGCGCTGTGAAAATCTCTTGAAAGAAAGAAACTGCTCAGACCCCTGGGGCCAGTCATGGGTACCAAGAA
AATAACAGGGGGCCCTGGCTTATCAACGGACGCCATGCTAAATTGGCACCGTGGTGTCTTCTTTGTAACAA
CTCCTATGTTCTTAGTGGCAATGAGAAAAGAACTTGCCAGCAGAATGGAGAGTGGTCAGGGAAACAGCCCACATG
CATAAAAGCCTGCCGAGAACCAAAGATTTCAGACCTGGTGGAGAAGGGAGAGTCTTCCGATGCGAGGTCAGTCAG
GGAGACACCATTACACCAGCTACTCAGCGGCCCTCAGCAAGCAGAAACTGCAGAGTCCCCCTACCAAGAACCC
AGCCCTCCCTTGAGATCTGCCATGGGATACCAACATCTGCATACCCAGCTCCAGTATGAGTGCATCTCACC
CTTCTACCGCCGCTGGCAGCAGCAGGAGGACATGTCAGGACTGGAAAGTGGAGTGGCGGGACCACATCTG
CATCCCTATCTGGGGAAATTGAGAACATCACTGCTCCAAAGACCAAGGGTTGCGCTGGCGTGGCAGGCAGC
CATCTACAGGAGGACCAGCGGGGTGCATGACGGCAGCCTACACAAGGGAGCGTGGTCTAGTCTGCAGCGGTGC
CCTGGTGAATGAGCGCACTGTGGTGGCTGCCACTGTGTTACTGACCTGGGAAGGTCACCATGATCAAGAC
AGCAGACCTGAAAGTTGGGAAATTCTACCGGGATGATGACCGGGATGAGAACCCATCCAGAGCCTACAC
GATTTCGCTATCATTCTGCATCCAACTATGACCCCATCCTGCTGATGCTGACATGCCATCCTGAAGCTCCT
AGACAAGGCCGTATCAGCACCCGAGTCCAGCCATCTGCCCTGCCAGTCGGGATCTCAGCACCTCCCT
GGAGTCCCACATCACTGTGGCTGGCTGGAATGTCCTGGCAGACGTGAGGAGCCCTGGCTTAAGAACGACACACT
GCGCTCGGGTGGTCACTGTGGTGGACTCGCTGCTGTGAGGAGCAGCATGAGGACCATGGCATCCAGTGAG
TGTCACTGATAACATGTTCTGTGCCAGCTGGAAACCCACTGCCCTCTGATATCTGCACTGCAGAGACAGGAGG
CATCGCGCTGTGTCCTCCGGACGAGCATCTCCTGAGCCACGCTGGCATCTGATGGACTGGTCAGCTGGAG
CTATGATAAAACATGCAGCCACAGGCTCTCCACTGCCTCACCAAGGTGCTGCCCTTAAAGACTGGATTGAAAG
AAATATGAAATGAACCAGTGCATGCACCTTGAGAAGTGTGTTCTGTATATCCGTCAGTGTGTCATTGCG
TGAAGCAGTGTGGCCTGAAAGTGTGATTGGCCTGTGAACCTGGCTGTGCCAGGGCTCTGACTTCAGGGACAAA
ACTCAGTGAAGGGTGAGTAGACCTCATTGCTGGTAGGCTGATGCCCGTCCACTACTAGGACAGCCAATTGGAA
GATGCCAGGGCTTGCAGAACAGTAAGTTCTCAAAGAACCCATATACAAACCTCTCCACTCCACTGACCTGGT
GGTCTTCCCCAACCTTCAGTTATACGAATGCCATCAGCTTGACCAGGGAGATCTGGCTCATGAGGCCCTT
TGAGGCTCTCAAGTTCTAGAGAGCTGCCGTGGAGCAGCCAGGGCAGCAGAGCTGGGATGTGGTGCATGCCCTT
GTGTACATGCCACAGTACAGTCTGGCCTTTCTCCCATCTTGTACACATTTAATAAAAAGGGTTG
GCTTCTGAACTACAA
AAA

FIGURE 38

MELGCWTQLGLTFLQLLLISSLPREYTVINEACPGAEWNIMCRECCEYDQIECVCPGKREVVG
YTIPCCRNEENECDSCLIHPGCTIFENCKSRNGSWGGTLDDFYVKGFYCAECRAGWYGGDCM
RCGQVLRAPKGQILLESYPLNAHCEWTIHAKPGFVIQLRFVMLSLEFDYMCQYDYVEVRGDN
RDGQIIKRVCVGNERPAPIQSIGSSLHVLFHSDGSKNFDGFHAIYEEITACSSSPCFHDGTCVL
DKAGSYKCACLAGYTGQRCENLLEERNCSDPGGPVNGYQKITGGPGLINGRHAKIGTVVSFFC
NNSYVLSGNEKRTCQQNGEWSGKQPIKACREP KISDLVRRVLPQMVSRETPLHQLYSAA
FSKQKLQSAPTKKPALPFQDLPMDGYQHLHTQLQYECISPFYRRLGSSRTCLRTGKWSGRAPS
CIPICGKIEINITAPKTQGLRWPWQAAIYRRRTSGVHDGSLHKGAFLVCSGALVNERTVVVAH
CVTDLGKVTMIKTADLKVVLGKFYRDDDDEKTIQSLQISAIILHPNYDPILLADIAILKLL
DKARISTRVQPICLAASRDLSTSFQESHITVAGWNVLADVRSPGFKNDSLRSGVVSVVDSLLC
EEQHEDHGIPVSVTDNMFCASWEPTAPS DICTAETGGIAAVSFPGRASPEPRWHLMGGLVWSY
DKTCSHRLSTAFTKVLPKDWIERNMK

Important features of the protein:

Signal peptide:

amino acids 1-23

EGF-like domain cysteine pattern signature.

amino acids 260-272

N-glycosylation sites.

amino acids 96-100, 279-283, 316-320, 451-455, 614-618

N-myristoylation sites.

amino acids 35-41, 97-103, 256-262, 284-290, 298-304, 308-314,
474-480, 491-497, 638-644, 666-672

Amidation site.

amino acids 56-60

Serine proteases, trypsin family.

amino acids 489-506

CUB domain proteins profile.

amino acids 150-167

FIGURE 39

GGTCCTACATCCTCATCTGAGAATCAGAGAGCATAATCTTCTACGGGCCGTGATTATTAACGTGGCTTA
ATCTGAAGGTTCTCAGTCAAATTCTTGTGATCTACTGATTGTGGGGCATGGCAAGGTTGCTAAAGGAGCTT
GGCTGGTTGGGCCCTGTAGCTGACAGAAGGTGGCAGGGAGAATGCAGCACACTGCTGGAGA**ATGAAGGCGC**
TTCTGTTGCTGGTCTTGCTTGGCTCAGTCTGCTAAGTACATTGACAATGTGGCAACCTGCACTTCCTGTATT
CAGAACTCTGTAAAGGTGCCTCCACTACGGCCTGACCAAAGATAGGAAGAGGCGCTCACAGATGGCTGTCCAG
ACGGCTGTGCGAGCCTCACAGCCACGGCTCCCTCCCCAGAGGTTCTGCAGCTGCCACCATCTCCTTAATGACAG
ACGAGCCTGGCCTAGACAACCTGCCTACGTGTCCTGGCAGAGGACGGCAGCCAGCAATCAGCCCAGTGGACT
CTGGCCGGAGCAACCGAACTAGGGCACGGCCCTTGAGAGATCCACTATTAGAAGCAGATCATTAAAAAAATAA
ATCGAGCTTGAGTGTCTCGAAGGACAAAGAGCAGGGAGTGCAGTTGCCAACCATGCCGACCAGGGCAGGGAAA
ATTCTGAAAACACCCTGCCCTGAAGTCTTCCAAGGTTGATCCACCTGATTCCAGATGGTGAATTACCAAGCA
TCAAGATCAATCGAGTAGATCCCAGTGAAGGCCTCTTATTAGGCTGGTGGAGGTAGCAGAACCCCCACTGGTCC
ATATCATTATCCAACACATTTATCGTGTGGGTGATGCCAGAGACGGCCGGCTACTGCCAGGAGACATCATT
TAAAGGTCAACGGGATGGACATCAGCAATGTCCTCACAACTACGCTGTGCGTCTCCTGCCAGCCCTGCCAGG
TGCTGTGGCTGACTGTGATGCGTGAACAGAAGTCCCGAGCAGGAACAATGGACAGGGCCGGATGCCCTACAGAC
CCCGAGATGACAGCTTCATGTGATTCTCAACAAAGTAGCCCCAGGAGCAGCTTGAATAAAACTGGTGC
AGGTGGATGAGCCTGGGTTTCATCTTCAATGTGCTGGATGGCGGTGTCATATGACATGGTCAGCTTGAGG
AGAATGACCGTGTGTTAGCCATCAATGGACATGATCTCGATATGGCAGCCCAGAAAGTGC
GGCTCATCTGAGCAGCTGGCCCCAGGGCCAGGGAGAGGAGCAACACTCCAAAGCCCCTCCATC
CAATTACTGTGATGAGAAGGTGTTAAATATCCAAAAGACCCGGTGAATCTCTGGCATGACCGTGCAGGG
GAGCATCACATAGAGAATGGATTGCTATCTATGTGATCAGTGTGAGCCCGAGGAGTCATAAGCAGAGATG
GAAGAATAAAACAGGTGACATTGTTGAATGTGGATGGGTCGAACAGAGGTGAGCCGGAGTGAGGAG
TGGCATTATTGAAAAGAACATCATCCTCGATAGTACTCAAAGCTTGGAGTCAAAGAGTATGAGCCCAGGAAG
ACTGCAGCAGCCCAGCAGCCCTGGACTCCAACCACAACATGGCCCAACCCAGTGACTGGCCCCATCCTGG
TGTGGCTGAAATTACCAACGGTGTGTTAACTGTAAAGATATTGTTACGAAGAAACACAGCTGGAGTCTGG
GCTTCTGCATTGTAGGAGTTATGAAGAATACAATGGAAACAAACCTTTTCAATCAAATCCATTGTTGAAGGAA
CACCAGCATACAATGATGGAAGAATTAGATGTGGTGAATTCTCTGCTGTCATGGTGAAGTACATCAGGAA
TGATACATGCTGCTTGGCAAGACTGCTGAAAGAACCTAAAGGAAGAATTACTCTAATCTTCTGGCTG
GCACCTTTT**ATAGA**ATCAATGATGGTCAGAGGAAACAGAAAATCACAATAGGCTAAGAAGTGTGAAACACT
ATATTATCTGTCAGTTTATATTAAAGAAAGAACATTGTAAGGAAAGTATGATCATCTAA
TGAAAGCCAGTTACACCTCAGAAAATGATTCCAAAAAAATTAAAATCTAGTTTTTCACTGTGGAGG
TTCTCATTACTCTACAACATTGTTATATTCTATTCAATAAAAGCCCTAAACAAACTAAAATGATTGATT
TGTATAACCCACTGAATTCAAGCTGATTAAATTAAAATGGTATATGCTGAAGTCTGCCAAGGGTACATT
GCCATTAAATTACAGCTAAATTTAAATGCATTGCTGAGAACGTTGCTTCATCAAACAAGAAT
AAATTTTCAGAAGTTAAA

40/168

FIGURE 40

MKALLLLVLPWLSPANYIDNVGNLHFLYSELCKGASHYGLTKDRKRRSQDGCPDGCASLTATA
PSPEVSAATISLMTDEPGLDNPAYVSSAEDGQPAISPVDGSRSNRARPFERSTIRSRFK
KINRALSVLRRTKSGAVANHADQGRENSENTTAPEVFPRLYHLIPDGEITSIKINRVDPSES
LSIRLVGGSETPLVHIIIQHIYRDGVIARDGRLLPGDIILKVNGMDISNVPHNYAVRLLRQPC
QVLWLTVMREQKFRSRNNGQAPDAYPRDDSFHVILNKSSPEEQLGIKLVRKVDEPGVIFNV
LDGGVAYRHGQLEENDRVLAINGHDLRYGSPESAAHLIQASERRVHLVVSQVRQSPDIFQE
AGWNSNGSWSPGPERSNTPKPLHPTITCHEKVVNIQKDPGESLGMTVAGGASHREWDLPIYV
ISVEPGGVISRDGRIKTGDILLNVDGVELTEVRSEAVALLKRTSSIVLKALEVKEYEPQED
CSSPAALDSNHNMAPPSDWSPSWVMWLELPRCLYNCKDIVLRRNTAGSLGFCIVGGYEEYNGN
KPFFIKSIVEGTPAYNDGRIRCGDILLAVNGRSTSGMIHACLLKELKGRITLTIVSWPGTFL

Important features:

Signal peptide:

amino acids 1-15

N-glycosylation sites.

amino acids 108-112, 157-161, 289-293, 384-388

Tyrosine kinase phosphorylation sites.

amino acids 433-441, 492-500

N-myristoylation sites.

amino acids 51-57, 141-147, 233-239, 344-350, 423-429, 447-453,
467-473, 603-609

FIGURE 41

ACCAGGCATTGTATCTCAGTTGTCATCAAGTTCGCAATCAGATTGGAAAAGCTCAACTGAA
GCTTCCTGCCTGCAGTGAAGCAGAGAGATAGATATTATTACGTAATAAAAACATGGGCTT
CAACCTGACTTCACCTTCCTACAAATTCCGATTACTGTTGCTGTTGACTTTGTGCCTGAC
AGTGGTTGGGTGGGCCACCAGTAACTACTTCGTGGGTGCCATTCAAGAGATTCTAAAGCAAA
GGAGTTCATGGCTAATTCCATAAGACCCCTCATTGGGAAGGGAAAAACTCTGACTAATGA
AGCATCCACGAAGAAGGTAGAACTTGACAACACTGCCTTCTGTCTCCTACCTCAGAGGCCA
GAGCAAGCTCATTTCAAACCAGATCTCACTTGGAAGAGGTACAGGCAGAAATCCCAAAGT
GTCCAGAGGCCGGTATGCCCTCAGGAATGTAAGCTTACAGAGGGTGCCTACCTCGTTCC
CCACCGGAACAGAGAGAAACACCTGATGTACCTGCTGGAACATCTGCATCCCTCCTGCAGAG
GCAGCAGCTGGATTATGGCATCTACGTACCCACCAGGCTGAAGGTAAAAGTTAATCGAGC
CAAACCTTGAAATGTGGCTATCTAGAACGCTCAAGGAAGAAAATTGGACTGCTTATATT
CCACGATGTGGACCTGGTACCGAGAATGACTTAACTTACAAGTGTGAGGAGCATCCAA
GCATCTGGTGGTGGCAGGAACAGCACTGGTACAGGTTACGTTACAGTGGATATTGGGGGG
TGTTACTGCCCTAACGAGAGAGCAGTTTCAAGGTGAATGGATTCTTAACAACACTGGGG
ATGGGGAGGCAGAACGATGACCTCAGACTCAGGGTTGAGCTCCAAAGAACATGAAAATTCCCG
GCCCTGCCTGAAGTGGTAAATATAACATGGTCTCCACACTAGAGAACAGAACAGATGGTTGAG
GAACGCAGAACGGATGAAGCTTACACCAAGTGTACGAGTCTGGAGAACAGATGGTTGAG
TAGTTGTTCTATAAATTAGTATCTGTGGAACACAATCCTTATATATCACACATCACAGTGG
TTTCTGGTTGGTGCATTGACCCTGGATCTTGGTATGTTGGAAGAACACTGATTCTTGT
GCAATAATTGGCCTAGAGACTTCAAATAGTAGCACACATTAAGAACCTGTTACAGCTCATT
GTTGAGCTGAATTTCTTTGTATTTCTTAGCAGAGCTCTGGTATGTAGAGTATAAA
ACAGTTGTAACAAGAACAGCTTCTTAGTCATTTGATCATGAGGGTAAATATTGTAATATGG
ATACTTGAAAGGACTTTATATAAAAGGATGACTCAAAGGATAAAATGAACGCTATTGAGGACT
CTGGTTGAAGGAGATTATTAAATTGAAAGTAATATATTATGGATAAAAGGCCACAGGAAA
TAAGACTGCTGAATGTCAGAGAACAGAGCTTCTCGTCCAAGGTAGAAAGGTACGAAGA
TACAATACTGTTATTCAATTATCCTGTACAATCATCTGTGAAGTGGTGGTGTAGGTGAGAAG
GCGTCCACAAAAGAGGGAGAAAAGGCAGGAATCAGGACACAGTGAACCTGGGAATGAAGAG
GTAGCAGGAGGGTGGAGTGTGGCTGCAAAGGCAGCAGTAGCTGAGCTGGTTGCAGGTGCTGA
TAGCCTTCAGGGAGGACCTGCCAGGTATGCCTCCAGTGATGCCACCAGAGAACATACATT
TCTATTAGTTAAAGAGTTTGTAAGGATGATTGTACAAGTAGGATATGAATTAGCAGT
TTACAAGTTACATATTAACATAAAATATGTCTATCAAACCTCTGTAGTAAATGTG
AAAAAGCAAAA

42/168

FIGURE 42

MGFNLTFHLSYKFRLLLLLTLCLTVVGWATSNYFVGAIQEIPKAKEFMANFHKTLLGKGKTL
TNEASTKKVELDNCPSVSPYLRGQSKLIFKPDLTLEEVQAENPKVSRGRYRPQECKALQRVAI
LVPHRNREKHLMYLLEHLHPFLQRQQLDYGIYVIHQAEKKFNRAKLLNVGYLEALKEENWDC
FIFHDVDLVPENDFNLYKCEEHPKHLVVGRNSTGYRLRYSGYFGGVTALSREQFFKVNGFSNN
YWGWGGE-DDDLRLRVELQRMKISRPLPEVGKYTMVFHTRDKGNEVNAERMKLLHQVSRVWRTD
GLSSCSYKLVSVEHNPLYINITVDFWFGA

Important features:

Signal peptide:

amino acids 1-27

N-glycosylation sites.

amino acids 4-8, 220-224, 335-339

Xylose isomerase proteins.

amino acids 191-202

FIGURE 43

GCTCAAGACCCAGCAGTGGGACAGCCAGACAGACGGCACGATGGCAC TGAGCTCCAGATCTG
GGCCGCTTGCCTCCTGCTCCTCCTCCTCGCCAGCCTGACCAGTGGCTCTGTTTCCCACA
ACAGACGGACAACTTGCAGAGCTGCAACCCAGGACAGAGCTGGAGCCAGGGCCAGCTGGAT
GCCCATGTTCCAGAGGCGAAGGAGGCGAGACACCCACTTCCCCTGCATTTCTGCTGCGG
CTGCTGTCATCGATCAAAGTGTGGATGTGCTGCAAGACGTAGAACCTACCTGCCCTGCC
GTCCCCCTCCCTCCTTATTATTCCCTGCTGCCAGAACATAGGTCTTGGAAATAAAATGGCTG
GTTCTTTGTTTCCAA
AA

44/168

FIGURE 44

MALSSQIWAACLLLLL~~ASLTSGSVFPQQTGQLAELQPQDRAGARASWM~~PMFQRRRRDTHF
PICIFCCGCCHRSKCGMCCKT

Important features:

Signal peptide:

amino acids 1-24

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 58-59

N-myristoylation site.

amino acids 44-50

Prokaryotic membrane lipoprotein lipid attachment site.

amino acids 1-12

FIGURE 45

GTGGCTTCATTCAGTGGCTGACTTCCAGAGAGCAATATGGGCTGGTCCCCAACATGCCTCAC
CCTCATCTATATCCTTGGCAGCTCACAGGGTCAGCAGCCTCTGGACCCGTGAAAGAGCTGGT
CGGTTCCGTTGGTGGGCCGTGACTTCCCCCTGAAGTCAAAGTAAAGCAAGTTGACTCTAT
TGTCTGGACCTTCAACACAAACCCCTTGTACCACAGCCAGAAGGGGGCACTATCATAGT
GACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCAGATGGAGGCTACTCCCTGAAGCTCAG
CAAACGTGAAGAAGAATGACTCAGGGATCTACTATGTGGGGATATACAGCTCATCACTCCAGCA
GCCCTCCACCCAGGAGTACGTGCTGCATGTCTACGAGCACCTGTCAAAGCCTAAAGTCACCAT
GGGTCTGCAGAGCAATAAGAATGGCACCTGTGTGACCAATCTGACATGCTGCATGGAACATGG
GGAAGAGGATGTGATTATACCTGGAAGGCCCTGGGGCAAGCAGCCAATGAGTCCCATAATGG
GTCCATCCTCCCCATCTCCTGGAGATGGGGAGAAAGTGATATGACCTCATCTGCCTGCCAG
GAACCCCTGTCAGCAGAAACTTCTCAAGCCCCATCCTGCCAGGAAGCTCTGTGAAGGTGCTGC
TGATGACCCAGATTCCCTCATGGCCTCCTGTGTCTCCTGTTGGTGCCCTCCTGCTCAGTCT
CTTGACTGGGCATTTCTGGTTCTGAAGAGAGAGACAAGAAGAGTACATTGAAGA
GAAGAAGAGAGTGACATTGTCGGAAACTCCTAACATATGCCCTATTCTGGAGAGAACAC
AGAGTACGACACAATCCCTCACACTAACAGAACATCCTAAAGGAAGATCCAGCAAATACGGT
TTACTCCACTGTGGAAATACCGAAAAAGATGGAAAATCCCCACTCACTGCTCACGATGCCAGA
CACACCAAGGCTATTGCCTATGAGAATGTTATCTAGACAGCAGTGCACTCCCTAAGTCTCT
GCTCA

FIGURE 46

MAGSPTCLTLIYILWQLTGSAASGPVKELVGSVGGAVTFPLKSKVKQVDSIVWTFNTTPLVTI
QPEGGTIIVTQNRRERVDFPDGGYSLKLSKLKKNDSGIYYVGIYSSSLQQPSTQEYVLHVYE
HLSKPVMTMGLQSNKNGTCVTNLTCMEHGEEDIYTWKALGQAANESHNGSILPISWRWGES
DMTFICVARNPVSRNFSSPILARKLCEGAADDPDSSMVLCLLLVPLLLSLFVLGLFLWFLKR
ERQEEYIEEKKRVDICRETPNICPHSGENTEYDTIPTHNRTILKEDPANTVYSTVEIPKKMEN
PHSLLTMDPTPRLFAYENVI

Important features:

Signal peptide:

amino acids 1-22

Transmembrane domain:

amino acids 224-250

Leucine zipper pattern.

amino acids 229-251

N-glycosylation sites.

amino acids 98-102, 142-146, 148-152, 172-176, 176-180, 204-208,
291-295

47/168

FIGURE 47

GGCTCGAGCGTTCTGAGCCAGGGTGACCATGACCTGCTGCGAAGGATGGACATCCTGCAAT
GGATTCAGCCTGCTGGTTCTACTGCTGTTAGGAGTAGTTCTCAATGCGATACCTCTAATTGTC
AGCTTAGTTGAGGAAGACCAATTCTCAAAACCCATCTCTGCTTGAGTGGTGGTCCCA
GGAATTATAGGAGCAGGTCTGATGCCATTCCAGCAACAACAATGTCCTGACAGCAAGAAAA
AGAGCGTGCTGCAACAACAGAACTGGAATGTTCTTCATCATTTCAGTGTGATCACAGTC
ATTGGTGCTCTGTATTGCATGCTGATATCCATCCAGGCTCTTAAAGGTCTCATGTG
AATTCTCCAAGCAACAGTAATGCCATTGTGAATTTCATTGAAAAACATCAGTGACATT
CCAGAACCTTCAACTGCAGTGGTTTCAATGACTCTTGTGCACCTCCTACTGGTTCAAT
AAACCCACCAAGTAACGACACCAGGCGAGTGGCTGGAGAGCATCTAGTTCCACTCGATT
GAAGAAAACAAACATAGGCTTATCCACTCTCAGTATTAGGTCTATTGCTTGGATT
CTGGAGGTCTGTTGGCTCAGTCAGATAGTCATCGGTTCCGGCTGTGTGGAGTC
TCTAACGGAAGAAGTCAAATTGTGTAGTTATGGAAATAAAATGTAAGTATCAGTAGTTGA
AAAAAAAAAA

FIGURE 48

MTCCEGWTSCNGFSLLVLLLLGVVLNAIPLIVSLVEEDQFSQNPISCFEWWFPGIIGAGLMAI
PATTMSLTARKRACCNRTGMFLSSFFSVITVIGALYCMLISIQALLKGPLMCNSPSNSNANC
EFSLKNISDIHPESFNLQWFFNDSCAPPTGFNKPTSNDTMASGWRASSHFDFSEENKHRLIHF
SVFLGLLLGVILEVLFGLSQIVIGFLGCLCGVSKRRSQIV

Important features:

Transmembrane domains:

amino acids 10-31 (type II), 50-72, 87-110, 191-213

N-glycosylation sites.

amino acids 80-84, 132-136, 148-152, 163-167

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 223-227

N-myristoylation sites.

amino acids 22-28, 54-60, 83-89, 97-103, 216-222

Prokaryotic membrane lipoprotein lipid attachment site.

amino acids 207-218

TNFR/NGFR family cysteine-rich region protein.

amino acids 4-12

FIGURE 49

ATCCGTTCTCTGCCTGCCAGCTCAGGTGAGCCCTGCCAAGGTGACCTCGCAGGACACTGGT
GAAGGAGCAGTGAGGAACCTGCAGAGTCACACAGTTGCTGACCAATTGAGCTGTGAGCCTGGA
GCAGATCCGTGGCTGCAGACCCCCGCCCCAGTGCCTCTCCCCCTGCAGCCCTGCCCTCGAA
CTGTGACATGGAGAGAGTGACCCCTGCCCTCTCCTACTGGCAGGCCTGACTGCCCTGGAAGC
CAATGACCCATTGCCAATAAGACGATCCCTCTACTATGACTGGAAAAACCTGCAGCTGAG
CGGACTGATCTGCAGGGCTCTGCCATTGCTGGATCGGGCAGTTCTGAGTGGCAAATG
CAAATACAAGAGCAGCCAGAAGCAGCACAGTCCTGTACCTGAGAAGGCCATCCACTCATCAC
TCCAGGCTCTGCCACTACTTGCTTGAGCACAGGACTGCCCTCCAGGGATGGCCTGAAGCCTAAC
ACTGGCCCCCAGCACCTCCTCCCCCTGGAGGCCTTATCCTCAAGGAAGGACTTCTCTCCAAGG
GCAGGCTTTAGGCCCTTCTGATCAGGAGGCTTCTTATGAATTAAACTGCCACCACC
CCCTCA

50/168

FIGURE 50

MERVTLALLLAGLTALEANDPFANKDDPFYYDWKNLQLSGLICGGLAIAGIAAVLSGKCKY
KSSQKQHSPVPEKAIPPLITPGSATTC

Important features:

Signal peptide:

amino acids 1-16

Transmembrane domain:

amino acids 36-59

N-myristoylation sites.

amino acids 41-47, 45-51, 84-90

Extracellular proteins SCP/Tpx-1/Ag5/PR-1/Sc7.

amino acids 54-67

FIGURE 51

GTGGACTCTGAGAAGCCCAGGCAGTTGAGGACAGGAGAGAAGGCTGCAGACCCAGAGGGAG
GGAGGACAGGGAGTCGAAGGAGGAGGACAGAGGAGGGCACAGAGACGCAGAGCAAGGGCGGC
AAGGAGGAGACCCTGGTGGGAGGAAGACACTCTGGAGAGAGAGGGGCTGGCAGAGATGAAG
TTCCAGGGGCCCTGGCCTGCCTGCTGGCCCTCTGCCTGGCAGTGGGAGGCTGGCC
CTGCAGAGCGGAGAGGAAAGCACTGGACAAATATTGGGAGGCCATTGGCAAAGAGGCCGGAGGGCAGCTGGCTCT
GACGCCCTGAGCGAAGGGTGGAAAGGCCATTGGCAAAGAGGCCGGAGGGCAGCTGGCTCT
AAAGTCAGTGAGGCCCTGGCCAAGGGACCAGAGAACAGCTGGCACTGGACTCAGGCAGGTT
CCAGGCTTGGCGCAGCAGATGCTTGGCAACAGGGCAGGGAAAGCAGCCCAGTCTGG
AACACTGGCACGAGATTGGCAGACAGGCAGAACAGATGTCATTGACACGGAGCAGATGCTGTC
CGCGGCTCCTGGCAGGGGTGCCTGCCACAGTGGCTGGAAACTCTGGAGGCCATGGC
ATCTTGGCTCTCAAGGTGGCCTGGAGGCCAGGGCAATCCTGGAGGTCTGGGACT
CCGTGGTCCACGGATACCCGGAAACTCAGCAGGCAGCTTGAATGAATCCTCAGGGAGCT
CCCTGGGTCAAGGAGGCAATGGAGGCCACCAAACCTTGGACCAACACTCAGGGAGCTGTG
GCCAGCCTGGCTATGGTCAGTGAGAGCCAGCAACCAGAACATGAAGGGTCACGAATCCCCA
CCATCTGGCTCAGGTGGAGGCCTCAGCAACTCTGGGGAGGCAGCGGCTCACAGTCGGCAGC
AGTGGCAGTGGCAGCAATGGTACAACAACATGGCAGCAGCAGTGGTGGCAGCAGCAGTGGC
AGCAGCAGTGGCAGCAGCAGTGGCGCAGCAGTGGCGCAGCAGTGGTGGCAGCAGTGGCAAC
AGTGGTGGCAGCAGAGGTGACAGCGGCAGTGAGTCCTCTGGGATCCAGCACCGCTCCTCC
TCCGGCAACCACGGTGGAGCGGGAGGAAATGGACATAAACCGGGTGTGAAAGCCAGGG
AATGAAGCCCGGGAGCGGGGAATCTGGATTCAAGGGCTTCAGAGGACAGGGAGTTCCAGC
AACATGAGGGAAATAAGCAAAGAGGCCATCGCCTCCTGGAGGCTCTGGAGACAATTATCGG
GGCAAGGGTCGAGCTGGGCAGTGGAGGAGGTGACGCTGTTGGAGTCATAACTGTGAAC
TCTGAGACGTCTCCTGGATGTTAACTTGACACTTCTGGAAGAATTTAAATCCAAGCTG
GGTTCATCAACTGGATGCCATAAACAGGACAGAGAAGCTCTGCATCCCGTGACCCTCCA
GACAAGGAGCCACCAGATTGGATGGAGGCCACACTCCCTCTTAAACACCACCCCTCTCA
TCACTAATCTCAGCCCTGCCCTGAAATAACCTTAGCTGCCACAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAA

FIGURE 52

MKFQGPLACLLLALCLGSGEAGPLQSGEESTGTNIGEALGHGLGDALSEGVGKAIGKEAGGAA
GSKVSEALGQGTREAVGTGVRQVPGFGAADALGNRVGEAAHALGNTGHEIGRQAEDVIRHGAD
AVRGSWQGVPGHSGAWETSGGHGIFGSQGGLGGQQGNPGGLGTPWVHGYPGNSAGSGFMNPQ
GAPWGQGGNGGPPNFGTNTQGAVAQPGYGSVRASNQNEGCTNPPPSGSGGGSSNSGGSGSQS
GSSGSGSNGDNNNGSSSGSSGSSGSSGGSSGGSSGSGSNGSGSRGDSGSESSWGSSTG
SSSGNHGGSGGGNGHKPGCEKPGNEARGSGESGIQGFRGQGVSSNMREISKEGNRLLGGSGDN
YRGQGSSWGSGGDAVGGVNTVNSETSPGMNFDTFWKNFKSKLGFINWDAINKDQRSSRIP

Signal peptide:

amino acids 1-21

N-glycosylation site.

amino acids 265-269

Glycosaminoglycan attachment site.

amino acids 235-239, 237-241, 244-248, 255-259, 324-328, 388-392

Casein kinase II phosphorylation site.

amino acids 26-30, 109-113, 259-263, 300-304, 304-308

N-myristoylation site.

amino acids 17-23, 32-38, 42-48, 50-56, 60-66, 61-67, 64-70,
74-80, 90-96, 96-102, 130-136, 140-146, 149-155, 152-158,
155-161, 159-165, 163-169, 178-184, 190-196, 194-200, 199-205,
218-224, 236-242, 238-244, 239-245, 240-246, 245-251, 246-252,
249-252, 253-259, 256-262, 266-272, 270-276, 271-277, 275-281,
279-285, 283-289, 284-290, 287-293, 288-294, 291-297, 292-298,
295-301, 298-304, 305-311, 311-317, 315-321, 319-325, 322-328,
323-329, 325-331, 343-349, 354-360, 356-362, 374-380, 381-387,
383-389, 387-393, 389-395, 395-401

Cell attachment sequence.

amino acids 301-304

FIGURE 53

GGAGAAGAGGTTGTGGACAAGCTGCTCCGACAGAAGG**ATG**TGCTGCTGAGCCTGCCCT
GGCTGGGCCTCAGACCGGTGGCAATGTCCCCATGGCTACTCCTGCTGGTTGTGGCTCCT
GGCTACTCGCCCGCATCCTGGCTGGACCTATGCCTTCTATAACAACCTGCCGCCGGCTCCAGT
GTTTCCCACAGCCCCAAAACGGAACCTGGTTGGGTCACCTGGCCTGATCACTCCTACAG
AGGAGGGCTTGAAGGACTCGACCCAGATGTCGGCCACCTATTCCCAGGGCTTACGGTATGGC
TGGGTCCCATCATCCCCTCATCGTTTATGCCACCCCTGACACCATCCGGTCTATCACCAATG
CCTCAGCTGCCATTGCACCCAAGGATAATCTCTTATCAGGTTCTGAAGCCCTGGCTGGAG
AAGGGATACTGCTGAGTGGCGGTGACAAGTGGAGCCGCCACCGTCGGATGCTGACGCCGCCT
TCCATTCAACATCCTGAAGTCCTATATAACGATCTCAACAAGAGTGCAAACATCATGCTTG
ACAAGTGGCAGCACCTGGCCTCAGAGGGCAGCAGTCGCTGGACATGTTGAGCACATCAGCC
TCATGACCTTGGACAGTCTACAGAAATGCATCTCAGCTTGACAGCCATTGTCAGGAGAGGC
CCAGTGAATATATTGCCACCATCTGGAGCTCAGTGCCCTGTAGAGAAAAGAACGCCAGCATA
TCCTCCAGCACATGGACTTCTGTATTACCTCTCCATGACGGCGGGCTTCCACAGGGCCT
GCCGCCTGGTGCATGACTCACAGACGCTGTCATCCGGAGCGGGCTCGCACCCCTCCCACTC
AGGGTATTGATGATTTTCAAAGACAAAGCCAAGTCCAAGACTTGATTTGATTGATGTGC
TTCTGCTGAGCAAGGATGAAGATGGGAAGGCATTGTCAGATGAGGATATAAGAGCAGAGGCTG
ACACCTTCATGTTGGAGGCCATGACACCACGGCCAGTGGCCTCTCCTGGGTCTGTACAACC
TTGCGAGGCACCCAGAATACCAGGAGCGCTGCCGACAGGAGGTGCAAGAGCTCTGAAGGACC
GCGATCCTAAAGAGATTGAATGGGACGACCTGGCCAGCTGCCCTCCTGACCATGTGCGTGA
AGGAGAGCCTGAGGTTACATCCCCCAGCTCCCTCATCTCCGATGCTGCACCCAGGACATTG
TTCTCCCAGATGGCGAGTCATCCCCAAAGGCATTACCTGCCTCATCGATATTATAGGGTCC
ATCACAACCCAACTGTGTGGCCGGATCCTGAGGTCTACGACCCCTCCGCTTGACCCAGAGA
ACAGCAAGGGGAGGTCACCTCTGGTTTATTCCCTCCGAGGGGCCAGGAACGTGACATCG
GGCAGGCAGTTCGCCATGGCGGAGATGAAAGTGGCCTGGCGTTGATGCTGCTGCACTCCGGT
TCCTGCCAGACCACACTGAGCCCCGAGGAAGCTGGAATTGATCATGCGCGCCAGGGCGGGC
TTGGCTGCGGGTGGAGCCCTGAATGTAGGCTTGCAG**TGA**CTTCTGACCCATCCACCTGTT
TTTTGCAGATTGTCATGAATAAAACGGTGTGTCAAA

FIGURE 54

MSLLSLPWGLRPVAMSPWLLLLLVGSWLLARILAWTYAFYNNCRRLQCFPQPPKRNWFWGH
LGLITPTEEGLKDSTQMSATYSQGFTVWLGPPIIPFIVLCHPDTIRSITNASAAIAPKDNLFIR
FLKPWLGEGLLGGDKWSRHRRLTPAFHFNILKSYITIFNKSANIMLDKWQHLASEGSSRL
DMFEHISLMTLDSLQKCIFSFDSHCQERPSEYIATILELSALVEKRSQHILQHMDFLYYLSHD
GRRFHACRLVHDFDAVIRERRRLPTQGIDDFFKDKAKSKTLDFIDVLLSKDEDGKALSD
EDIRAEADTFMFGGHDTTASGLSWVLYNLRHPEYQERCRCQEVQELLKDRDPKEIEWDDLAQL
PFLTMCVKESLRLHPPAPFISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNPTVWPDPEVYD
PFRFDPENSKGRSPLAFIPFSAGPRNCIGQAFAMAEMKVVLALMLHFRFLPDHTEPRRKLEL
IMRAEGGLWLRVEPLNVGLQ

Important features:

Transmembrane domains:

amino acids 13-32 (type II), 77-102

Cytochrome P450 cysteine heme-iron ligand signature.

amino acids 461-471

N-glycosylation sites.

amino acids 112-116, 168-172

FIGURE 55

ATCGCATCAATTGGGAGTACCATCTTCCTC**ATG**GGACCAGTGAAACAGCTGAAGCGAATGTTT
GAGCCTACTCGTTGATTGCAACTATCATGGTGCTGTTGTTGCACTTACCCCTGTGTTCT
GCCTTTGGTGGCATAACAAGGGACTTGCACTTATCTTCTGCATTTGCAGTCTTGGCATTG
ACGTGGTACAGCCTTCCTCATACCATTGCAAGGGATGCTGTGAAGAAGTGTGTTGCCGTG
TGTCTTGCAT**TAAT**CATGCCAGTTTATGAAGCTTGGAAAGGCACTATGGACAGAAGCTGGT
GGACAGTTTGTAACTATCTCGAAACCTCTGTCTTACAGACATGTGCCTTTATCTTGCAGC
AATGTGTTGCTTGTGATTGAAACATTGAGGGTTACTTTGAAAGCAACAATACATTCTCGAA
CCTGAATGTCAGTAGCACAGGATGAGAAGTGGTTCTGTATCTGTGGAGTGGAAATCTTCCTC
ATGTACCTGTTCCCTCTGGATGTTGTCCCCTGAATTCCCATGAATAACAAACCTATTCA
AACAGCAAA
AAAAAAAAAAAAAA

56/168

FIGURE 56

MGPVKQLKRMFEPTRLIATIMVLLCFALTLCASFWWHNKGALIFCILQSLALTWYSLSFIPF
ARDAVKKCFAVCLA

Important features:

Signal peptide:

amino acids 1-33

Type II fibronectin collagen-binding domain protein.

amino acids 30-72

FIGURE 57

CGGCTCGAGCTCGAGCCGAATCGGCTCGAGGGCAGTGGAGCACCCAGCAGGCCAAC**ATG**CTCTGTCTGTGC
CTGTACGTGCCGGTCATCGGGGAAGCCCAGACCGAGTCCAGTACTTGAGTCGAAGGGGCTCCCTGCCGAGCTG
AAGTCCATTTCAGCTCAGTGTCTCATCCCCTCCAGGAATTCTCCACCTACCGCCAGTGGAAAGCAGAAAATT
GTACAAGCTGGAGATAAGGACCTTGATGGCAGCTAGACTTGAAGAATTGTCCATTATCTCAAGATCATGAG
AAGAAGCTGAGGCTGGTGTAAAGATTTGACAAAAGAATGATGGACGCATTGACGCGCAGGAGATCATGCAG
TCCCTGCCGGACTTGGGAGTCAAGATATCTGAACAGCAGGCAGAAAAATTCTCAAGAGCATGGATAAAAACGGC
ACGATGACCATCGACTGGAACGAGTGGAGAGACTACCAACCTCCACCCCGTGGAAAACATCCCGAGATCATC
CTCTACTGGAAGCATTCCACGATCTTGATGTGGTGGAGAATCTAACGGTCCCGATGAGTTACAGTGGAGGAG
AGGCAGACGGGGATGTGGTGGAGACACCTGGTGGCAGGGAGGTGGGGCAGGGGCCGTATCCAGAACCTGCACGGCC
CCCCCTGGACAGGCTCAAGGTGCTCATGCAGGTCCATGCCCTCCCGCAGCAACAACATGGGATCGTTGGCTTC
ACTCAGATGATTGAGAAGGAGGGCCAGGTCACTCTGGGGGCAATGGCATCAACGTCTCAAATTGGCCCC
GAATCAGGCCATCAAATTCTGGCCTATGAGCAGATCAAGGCCCTTGTGGTAGTGACAGGAGACTCTGAGGATT
CACAGAGAGGCTGTGGCAGGGCTTGGCAGGGGCCATGCCAGAGCAGCATCACCAATGGAGGTCTGAAG
ACCCGGATGGCGCTGCGGAAGACAGGCCAGTACTCAGGAATGCTGGACTGCCAGGGAGATCTGGCCAGAGAG
GGGGTGGCCGCCCTCTACAAAGGCTATGTCCCCAACATGCTGGCATTGCCCTATGCCGGCATCGACCTTGCA
GTCTACGAGACGCTCAAGAATGCCCTGGCTGCACTATGCACTGAACAGCGCGGACCCCGTGTGGCTC
CTGGCCTGTGGCACCATGTCCAGTACCTGTGGCCAGCTGGCCAGCTACCCCTGGCCCTAGTCAGGACCCGGATG
CAGCGCAAGCCTTATTGAGGGCGCTCCGGAGGTGACCATGAGCAGCCTTCAAACATATCTGCGGACCGAG
GGGGCCTTCGGGCTGTACAGGGGCTGGCCCCAACCTCATGAAGGTATCCCAGCTGTGAGCATCAGCTACGTG
GTCTACGAGAACCTGAAGATCACCTGGCGTGCAGTCGG**TG**ACGGGGGAGGGCCGCCAGTGGACTCG
CTGATCCTGGCCGCAGCCTGGGTGTGCAGCCATCTCATTCTGTGAATGTGCCAACACTAACGTGCTCGAGCC
AAGCTGTAAAACCCCTAGACGCACCCGCAGGGAGGGTGGGGAGAGCTGGCAGGCCAGGGCTTGTCTGCTGACC
CCAGCAGACCCCTCTGTGGTCCAGCGAAGACACAGGCATTCTTAGGGTCCAGGGTCAGCAGGCTCCGGCT
CACATGTGTAAGGACAGGACATTCTGCACTGCCTGCCAATAGTGAAGCTGGAGCCTGGAGGGCGCTTAGTTC
TTCCATTTCACCCCTGCAGCCAGCTGTGGCACGCCCTGCCCTCTGGCTGCCGTGCATCTCCCTGTGCCCT
CTTGCTGCCTGCCTGTGCTGAGGTAAGGTGGAGGGCTACAGCCCACATCCCACCCCTGTCCAATCCC
ATAATCCATGATGAAAGGTGAGGTACGTGCCCTCCAGGCTGACTTCCAAACCTACAGCATTGACGCCAACTT
GGCTGTGAAGGAAGAGGAAAGGATCTGGCCTTGTGGTCACTGGCATCTGAGCCCTGCTGATGGCTGGGCTCTCG
GGCATGCTTGGAGTGCAAGGGGCTCGGGCTGCCCTGGCTGACAGAAGGCAAGTGTGGGGCTCATGGTG
CTCTGAGCTGGCCTGGACCCCTGTGAGGATGGGCCACCTCAGAACCAAACACTACTGTCCCCACTGTGGCATGAG
GGCAGTGGAGCACCATGTTGAGGGCGAAGGGCAGAGCCTGGTGTGTTCTGGGGAGGGAAAGGAAAAGGTGTTGG
AGGCTTAATTATGGACTGTGGAAAAGGGTTTGTGAGGAAAGGACAAGCCGGACAAATGAGCGACTTCTGTGCT
TTCCAGAGGAAGACGAGGGAGCAGGAGCTGGCTGACTGCTCAGACTGTGCTGACGCCCTGGGGTTCTGTGCT
CAACCCAGCAGGGCGCAGCGGGACCAGCCCCACATTCACTTGTGTCAGTGGAACTATTATTGTA
TTTATTGAAACAGAGTTATGCTTAACATTATTATAGATTGTTAATTAAATAGCTTGTCAATTCAAGTTCAT
TTTTATTGATATTGTTATGCTGAGGAAAGGCTTGTGAGGAAATTCTTGTGAGGGACTGGAGGCAGAAAAGCGGCCAG
AAGGCAGCAGCCCTGGCTCTTCCCTGGCAGGTTGGGAAGGGCTGCCCTAGCCTTAGGATTTCAGGGTTT
GACTGGGGCGTGGAGAGAGAGGGAGGAACCTCAATAACCTGAAGGTGGAATCCAGTTATTCTGCGCTGCGA
GGGTTCTTATTCACTCTTCTGAATGTCAGGCAGTGGCTGCCCTCCAGCCTCTGCTGCCCTGCTTAACAATGCCGCCAA
GGCTGGAGGGAGGGTGGGGGCTGGCTCCCTCCAGCCTCTGCTGCCCTGCTTAACAATGCCGCCAA
CTGGCGACCTCACGGTTGCACTCCATTCCACCGAGAATGACCTGATGAGGAAATCTCAATAGGATGCAAAGATC
AATGCAAAATTGTTATATGAACATATAACTGGAGTCGTCAAAAGCAAATTAAAGAAAGAATTGGACGTTAGA
AGTGTGTCATTAAAGCAGCCTCTAATAAGTTGTTCAAAGCTGAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 58

MLCLCLYVPVIGEAQTEFQYFESKGLPAELKSIFKLSVFIPSQEFSTYRQWKQKIVQAGDKDL
DGQLDFEEFVHYLQDHEKKRLVFKILDKKNDGRIDAQEIMQSLRDLGVKISEQQAEKILKSM
DKNGTMTIDWNEWRDYHLLHPVENIPEIILYWKHSTIFDVGENLTVPDEFTVEERQTGMWWRH
LVAGGGAGAVSRTCTAPLDRLKVLMQVHASRSNNMGIVGGFTQMIREGGARSLWRGNGINVLK
IAPESAIKFMAYEQIKRLVGSDQETLRIHERLVAGSLAGAIAQSSIYPMEVLKTRMALRKTGQ
YSGMLDCARRILAREGVAAFYKGYVPNMLGIIPYAGIDLAVYETLKNAWLQHYAVNSADPGVF
VLLACGTMSSCGQLASYPLALVRTRMQAQASIEGAPEVTMSSLFKHILRTEGAFGLYRGLAP
NFMKVIPAVSISYVVYENLKITLGVQSR

Important features:

Signal peptide:

amino acids 1-16

Putative transmembrane domains:

amino acids 284-304, 339-360, 376-394

Mitochondrial energy transfer proteins signature.

amino acids 206-215, 300-309

N-glycosylation sites.

amino acids 129-133, 169-173

Elongation Factor-hand calcium-binding protein.

amino acids 54-73, 85-104, 121-140

FIGURE 59

GGAAGGCAGCGGCAGCTCCACTCAGCCAGTACCCAGATACTGGAAACCTCCCCAGCC**ATG**
GCTTCCCTGGGGCAGATCCTCTTCTGGAGCATAATTAGCATCATCATTATTCTGGCTGGAGCA
ATTGCACTCATCATTGGCTTGGTATTCAGGGAGACACTCCATCACAGTCACTACTGTCGCC
TCAGCTGGAACATTGGGAGGATGGAATCCTGAGCTGCACTTTGAACCTGACATCAAACCT
TCTGATATCGTATAACATGGCTGAAGGAAGGTTTAGGCTGGTCCATGAGTTCAAAGAA
GGCAAAGATGAGCTGTCGGAGCAGGATGAAATGTTCAGAGGCCGGACAGCAGTGTGCTGAT
CAAGTGATAGTTGGCAATGCCCTTTGGCTGAAAAACGTGCAACTCACAGATGCTGGCACC
TACAAATGTTATATCATCACCTCTAAAGGCAAGGGAAATGCTAACCTGAGTATAAAACTGGA
GCCTTCAGCATGCCGGAAAGTGAATGTGGACTATAATGCCAGCTCAGAGACCTTGCAGGTGTGAG
GCTCCCCGATGGTCCCCCAGCCCACAGTGGCTGGCATCCAAAGTTGACCAGGGAGCCAAC
TTCTCGGAAGTCTCCAATACCAAGCTTGGACTGAACTCTGAGAATGTGACCATGAAGGTTGTG
TCTGTGCTCTACAATGTTACGATCAACAAACACATACTCCTGTATGATTGAAAATGACATTGCC
AAAGCAACAGGGATATCAAAGTGACAGAATCGGAGATCAAAGGCCGGAGTCACCTACAGCTG
CTAAACTCAAAGGCTCTGTGTCTCTTCTTGCATCAGCTGGCAGCTTCTGCCT
CTCAGCCCTTACCTGATGCTAAAAT**TA**ATGTGCCTTGGCCACAAAAAGCATGCAAAGTCATTG
TTACAACAGGGATCTACAGAACTATTCACCACAGATATGACCTAGTTATATTCTGGGA
GGAAATGAATTCATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCAAGAAACAAAAAGGCC
AAAAGCAGAAGGCTCCAATATGAACAAGATAATCTATCTTCAAAGACATATTAGAAGTTGGG
AAAATAATTCATGTGAACTAGACAAGTGTGTTAAGAGTGATAAGTAAAATGCACGTGGAGACA
AGTGCATCCCCAGATCTCAGGGACCTCCCCCTGCCTGTCACCTGGGAGTGAGAGGACAGGAT
AGTGCATGTTCTTGTCTGAAATTTAGTTATATGCTGTAATGTTGCTCTGAGGAAGCC
CCTGGAAAGTCTATCCAACATATCCACATCTTATATCCACAAATTAGCTGTAGTATGTAC
CCTAAGACGCTGCTAATTGACTGCCACTTCGCAACTCAGGGCGGCTGCATTTAGTAATGGG
TCAAATGATTCACTTTATGATGCTCCAAAGGTGCCTTGGCTCTTCCAACTGACAAA
TGCCAAAGTTGAGAAAATGATCATAATTTAGCATAAACAGAGCAGTCGGGGACACCGATTT
TATAAATAAACTGAGCACCTCTTTAAACAAAAA
AAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAA

60/168

FIGURE 60

MASLGQILFWSIISIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDIK
LSDIVIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTDAG
TYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPQPTVVWASQVDQGA
NFSEVSNTSFELNSENVTMKVSVLYNVTINNTYSCMIENDIAKATGDIKTESEIKRRSHLQ
LLNSKASLCVSSFFAISWALLPLSPYMLK

Important features:

Signal peptide:

amino acids 1-28

Transmembrane domain:

amino acids 258-281

N-glycosylation sites.

amino acids 112-116, 160-164, 190-194, 196-200, 205-209, 216-220,
220-224

N-myristoylation sites.

amino acids 52-58, 126-132, 188-194

FIGURE 61

TGACGTCAGAATCACCAATGCCAGCTATCCTTACCGGCAGGGCTGCCAGGAGCTGCAGGACA
AGCACCAGGAGCCCTCCGGGTAGCTACTACCCTGGACCCCCAATAGTGGAGGGCAGTATGG
TAGTGGCTACCCCTGGTGGTATGGGGTCCCTGCCCTGGAGGGCCTATGGACCACC
AGCTGGTGGAGGGCCCTATGGACACCCAATCCTGGATGTTCCCTCTGGAACCTCAGGAGG
ACCATATGGCGGTGCAGCTCCGGGGCCCTATGGTCAGCCACCTCCAAGTTCCCTACGGTGC
CCAGCAGCCTGGGCTTATGGACAGGGTGGCGCCCTCCAATGTGGATCCTGAGGCCTACTC
CTGGTCCAGTCGGTGGACTCAGATCACAGTGGCTATATCTCCATGAAGGAGCTAACAGGC
CCTGGTCAACTGCAATTGGTCTTCATTCAATGATGAGACCTGCCTCATGATGATAAACATGTT
TGACAAGACCAAGTCAGGCCGCATCGATGTCTACGGCTCTCAGCCCTGTGGAAATTCCATCCA
GCAGTGGAAAGAACCTTTCCAGCAGTATGACCGGGACCGCTGGGCTCCATTAGCTACACAGA
GCTGCAGCAAGCTCTGCCAACGCTCTGCCATGCAGCTGACCCAGTTCCAGGTGTG
CTCCCGCTACTGCCAACGCTCTGCCATGCAGCTGACCCAGTTCCAGGTGTG
CACCCAGCTGCAGGTGCTGACAGAGGCCTCCGGAGAAGGACACAGCTGTACAAGGCAACAT
CCGGCTCAGCTCGAGGACTCGTACCATGACAGCTCTCGGATGCTTGACCAACCATCT
GTGGAGAGTGGAGTGCACCAGGGACCTTCCTGGCTTCTAGAGTGAGAGAAGTATGTGGACA
TCTCTTCTTCCCTGTCCTCTAGAAGAACATTCTCCCTGCTTGATGCAACACTGTTCCAAA
AGAGGGTGGAGAGTCCTGCATCATGCCACCAAATAGTGAGGACCGGGCTGAGGCCACACAG
ATAGGGGCCTGATGGAGGAGAGGATAGAAGTTGAATGTCCTGATGCCATGAGCAGTTGAGTG
GCACAGCCTGGCACCAGGAGCAGGTCTTGTAAATGGAGTTAGTGTCCAGTCAGCTGAGCTCCA
CCCTGATGCCAGTGGTAGTGTTCATGGCCTGTTACCGTTAGTACCTGTGTTCCCTCACCAG
GCCATCCTGTCAAACGAGCCCATTCTCAAAGTGAATCTGACCAAGCATGAGAGAGATCT
GTCTATGGGACCAGTGGCTGGATTCTGCCACACCCATAAATCCTGTGTTAACTTCTAGC
TGCCTGGGCTGGCCCTGCTCAGACAAATCTGCTCCCTGGCATCTTGGCAGGCTCTGCC
CCCTGCAGCTGGACCCCTCACTGCCATGCTGCTGGCTTCAGTCTCCAGGAGACA
GTGGTCACCTCTCCCTGCCAATACTTTTTAATTGCATTTTTCAATTGGGCCAAAAG
TCCAGTGAAATTGTAAGCTCAATAAAAGGATGAAACTCTGA

62/168

FIGURE 62

MASYPYRQCPGAAGQAPGAPPGSYYPGPPNSGGQYGSGLPPGGYGGPAPGGPYGPPAGGGP
YGHPNPGMFPSSGTGGPYGGAAPGGPYGQPPPSSYGAQQPGLYQOGGAPPNDPEAYSWFQSV
DSDHSGYISMKELKQALVNCNWSSFNDETCLMMINMFDKTKSGRIDVYGFSAWKFIQQWKNL
FQQYDRDRSGSISYTELQQALSQMGYNLSPQFTQLLVSRYCPRSANPAMQLDRFIQVCTQLQV
LTEAFREKDTAVQGNIRLSFEDFVTMTASRML

Important features of the protein:

Signal peptide:

amino acids 1-19

N-glycosylation site.

amino acids 147-150

Casein kinase II phosphorylation sites.

amino acids 135-138, 150-153, 202-205, 271-274

N-myristoylation sites.

amino acids 9-14, 15-20, 19-24, 33-38, 34-39, 39-44, 43-48, 61-66, 70-75, 78-83, 83-88, 87-92, 110-115

FIGURE 63

CAGG**ATG**CAGGGCCCGTGGCAGGGAGCTGCGCTCCTCTGGGCCTGCTCCTGGTCTGTCTTCA
TCTCCCAGGCCTTTGCCCGGAGCAGCTGGTGTGGAGGAGAAAGTTCCCAAAACTCGG
GACCAACTTGCCTCAGCTCGAACCTCCACTGGCCCTCTAACTCTGAACATCCGCA
GCCCGCTCTGGACCCAGGTCTAATGACTTGGCAAGGGTCCCTGAAGCTCAGCGTGCCTCC
ATCAGATGGCTTCCCACCTGCAGGAGGTTCTGCAGTGCAGAGGTGGCCTCCATCGTGGGGCT
GCCTGCCATGGATTCTGGCCCCCTGAGGATCCTTGGCAGATGATGGCTGCTGCGGCTGAGGA
CCGCCTGGGGAAAGCGCTGCCTGAAGAACTCTTACCTCTCAGTGCCTGCCCTCGCTCC
GGGCAGTGGCCCTTGCCTGGGAGTCTTCTCCGATGCCACAGGCCTCTCACCTGAGGCTTC
ACTCCTCCACCAAGGACTCGGAGTCCAGACGACTGCCCGTTCTAATTCACTGGGAGCCGGGG
AAAAATCCTTCCAACGCCCTCCCTGGTCTCTCATCCACAGGGTCTGCCTGATCACCCCTG
GGGTACCCCTGAATCCCAGTGTGCTGGGAGGTGGAGGCCCTGGACTGGTGGGAACGAG
GCCCATGCCACACCCCTGAGGAATCTGGGTATCAATAATCAACCCCCAGGTACCAGCTGGGG
AAATATTAATCGGTATCCAGGAGGCAGCTGGGAAATATTAATCGGTATCCAGGAGGCAGCTG
GGGAATATTAATCGGTATCCAGGAGGCAGCTGGGAAATATTCAATCTATACCCAGGTATCAA
TAACCCATTCCCTGGAGTTCTCCGCCCTCCTGGCTCTTGGAACATCCCAGCTGGCTT
CCCTAACCTCCAAGCCCTAGGTTGCAGTGGGC**TAG**AGCACGATAGAGGGAAACCCAACATT
GGGAGTTAGAGTCCTGCTCCGCCCTTGCTGTGTGGCTCAATCCAGGCCCTGTTAACATGT
TTCCAGCACTATCCCCACTTTCAAGTGCCTCCCTGCTCATCTCAATAAAATAAAAGCACTT
ATGAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

64/168

FIGURE 64

MQGRVAGSCAPLGLLVCLHLPGLFARSIGVVEEKVSQNFGTNLPQLGQPSSTGPSNSEHPQP
ALDPRSNDLARVPLKLSVPPSDGFPAGGSAVQRWPPSWGLPAMDSWPPEDPWQMMAAAEDR
LGEALPEELSYLSSAAALAPGSGPLPGEESP DATGLSPEASLLHQDSESRRLPRSNSLGAGGK
ILSQRPPWSLIHRVLPDHPWGTLNPSVSWGGGGPGTGWGTRPMPHPEGIWGGINNQPPGTWGN
INRYPGGSWGNINRYPGGSWGNINRYPGGSWGNIHLYPGINNPFPPGVLRPPGSSWNIPAGFP
NPPSPRLQWG

Important features of the protein:

Signal peptide:

amino acids 1-26

Casein kinase II phosphorylation sites.

amino acids 56-59, 155-158

N-myristoylation sites.

amino acids 48-53, 220-225, 221-226, 224-229, 247-252, 258-263,
259-264, 269-274, 270-275, 280-285, 281-286, 305-310

65/168

FIGURE 65

AAGGAGAGGCCACCGGGACTTCAGTGTCTCCTCCATCCCAGGAGCGCAGTGGCCACTATGGGG
TCTGGGCTGCCCTGTCCTCCTCTTGACCCCTCCTGGCAGCTCACATGGAACAGGGCCGGGT
ATGACTTGCAACTGAAGCTGAAGGAGTCTTCTGACAAATTCCCTATGAGTCCAGCTTC
CTGGAATTGCTTGAAAAGCTCTGCCTCCTCCATCTCCCTCAGGGACCAGCGTCACCCTC
CACCATGCAAGATCTAACACCATGTTGCTGCAACACATGACAGCCATTGAAGCCTGTGTCC
TTCTGGCCCGGGCTTTGGGCCGGGATGCAGGAGGCAGGCCCGACCCTGTCTTCAGCAG
GCCCCCACCCCTGAGTGGCAATAAAATTGGTATGCTG

66/168

FIGURE 66

MGSGLPLVLLTLLGSSHGTGPGMTLQLKLKESFLTNSSYESSFLELLEKLCLLLHLPSGTSV
TLHHARSQHHVVCNT

Important features:

Signal peptide:

amino acids 1-19

N-glycosylation site.

amino acids 37-41

N-myristoylation sites.

amino acids 15-21, 19-25, 60-66

67/168

FIGURE 67

ACGGACCGAGGGTTCGAGGGAGGGACACGGACCAGGAACCTGAGCTAGGTCAAAGACGCCGG
GCCAGGTGCCCGTCGCAGGTGCCCTGGCCGGAGATGCGGTAGGAGGGCGAGCGCGAGAAG
CCCCTCCTCGGCCTGCCAACCCGCCACCCAGCCCATGGCAGACCCGGCTGGGCTGCTT
CTGGCGCTGGGCCTGCCGTTCTGCTGGCCCGCTGGGGCCGAGCCTGGGGCAAATACAGACC
ACTTCTGCAAATGAGAATAGCACTGTTTGCCTCATCCACCAGCTCCAGCTCCGATGGCAAC
CTGCGTCCCGAAGCCATCACTGCTATCATCGTGGTCTTCTCCCTTGGCTGCCTGCTCCTG
GCTGTGGGCTGGCACTGTTGGTGCAGCTTCGGAGAAGCGGCAGACGGAGGGCACCTAC
CGGCCAGTAGCGAGGAGCAGTTCTCCATGCAGCCGAGGCCGGCCCTCAGGACTCCAAG
GAGACGGTGCAGGGCTGCCATCTAGGTCCCCCTCCTGCATCTGTCTCCCTTATTGC
TGTGTGACCTTGGGAAAGGCAGTGCCCTCTGGGCAGTCAGATCCACCCAGTGCTTAATAG
CAGGGAAAGAAGGTACTTCAAAGACTCTGCCCTGAGGTCAAGAGAGGATGGGCTATTCACTT
TTATATATTTATATAAAATTAGTAGTGAGATGTAAAAAAAAAAAAAA

68/168

FIGURE 68

MANPGLGLLLALGLPFLARWGRAWGQIQTTSANENSTVLPSSSTSSSDGNLRPEAITAIIVV
FSLLAALLLAVGLALLVRKLREKRQTEGTYRPSSEQFSHAAEARAPQDSKETVQGCLPI

Important features:

Signal peptide:

amino acids 1-19

Transmembrane domain:

amino acids 56-80

N-glycosylation site.

amino acids 36-40

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 86-90

Tyrosine kinase phosphorylation site.

amino acids 86-94

N-myristoylation sites.

amino acids 7-13, 26-32

FIGURE 69

GGCAGGAATAACTAGAGAGGAACAAATGGGGTTATTCAGAGGTTTGTTCCTCTTAGTTCTGTGCCTGCTGCAC
CAGTCAAATACCTCCTCATTAAGCTGAATAATAATGGCTTGAAAGATATTGTCTAGTTATAGATCCTAGTGTG
CCAGAAGATGAAAAAATAATTGAACAAATAGAGGATATGGTACTACAGCTTCTACGTACCTGTTGAAGCCACA
GAAAAAAGATTTTCAAAAATGTATCTATATTAAATTCTGAGAATTGAAAGGAAAATCCTCAGTACAAAAGG
CCAAAACATGAAAACCATAAACATGCTGATGTTATAGTTGCACCACCTACACTCCAGGTAGAGATGAACCACAC
ACCAAGCAGTTACAGAATGTGGAGAGAAAGGCGAATACATTCACTTCACCCCTGACCTCTACTTGGAAAAAAA
CAAAATGAATATGGACCAACCAGGAAACTGTTGTCCATGAGTGGCTCACCTCCGGTGGGAGTGTGTTGATGAG
TACAATGAAGATCAGCCTTCTACCGTGCTAAGTCAAAAAAATCGAAGCAACAAGGTGTTCCGCAGGTATCTCT
GGTAGAAATAGAGTTATAAGTGTCAAGGAGGCAGCTGTCTTAGTAGAGCATGCAGAATTGATTCTACAACAAA
CTGTATGGAAAAGATTGTCAATTCTTCTGATAAAAGTACAAACAGAAAAGCATCCATAATGTTATGCAAAGT
ATTGATTCTGTTGTTGAATTGTAACGAAAACCCATAATCAAGAAGCTCCAAGCCTACAAAACATAAAAGTGC
AATTTAGAAGTACATGGGAGGTGATTAGCAATTCTGAGGATTAAAACACCATAACCATGGTACACCCACCT
CCTCCACCTGTCTTCATTGCTGAAGATCAGTCAAAAGAATTGTTGCTTAGTTCTGATAAGTCTGGAAGCATG
GGGGTAAGGACCGCTAAATCGAATGAATCAAGCAGCAAAACATTCTGCTGCAGACTGTTGAAAATGGATCC
TGGTGGGGATGGTCACTTGTAGTAGTACTGCCACTATTGTAATAAGCTAATCCAAATAAAAAGCAGTGATGAA
AGAAACACACTCATGGCAGGATTACCTACATATCCTCTGGGAGGAACCTCCTGACTCTGCTGACTGATGGGAGGATAAC
ACTGCAAGTTCTGTATTGATGAAGTGAACAAAGTGGGGCATTGTTCTTATTGCTTGGGAAGAGCTGCT
GATGAAGCAGTAATAGAGATGAGCAAGATAACAGGAGGAAGTCATTGTTATGTTGATGAAGCTCAGAACAAAT
GGCTCTATTGATGCTTTGGGCTCTTACATCAGGAAATACTGATCTCTCCAGAACAGTCCCTCAGCTCGAAAGT
AAGGGATTAACACTGAATAGTAATGCTGGATGAACGACACTGTCATAATTGATAGTACAGTGGAAAGGACACG
TTCTTCTCATCACATGGAACAGTCTGCCTCCCAGTATTCTCTGTTGCTGACTGCTGTTCTGAAATCAGAACAAATGGAAAAT
TTCACAGTGGATGCAACTTCCAAATGGCTATCTAGTATTCCAGGAACAGTCAAAGGTGGGCACTTGGGCATAC
AATCTCAAGCCAAAGCGAACCCAGAAACATTAACATTACAGTAACCTCTCGAGCAGCAAATTCTGCTGCCT
CCAATCACAGTGAATGCTAAATGAATAAGGACGTAACAGTTCCCCAGCCCAATGATTGTTACGCAGAAATT
CTACAAGGATATGTACCTGTTCTGGAGCCAATGTGACTGCTTCTGAAATCACAGAACATACAGAACAGTT
TTGGAACTTTGGATAATGGTGCAAGCGCTGATTCTTCAAGAATGATGGAGTCACTCCAGGTATTTACAGCA
TATACAGAAAATGGCAGATATAGCTAAAAGTTGGGCTCATGGAGGAGCAAACACTGCCAGGCTAAAATACGG
CCTCCACTGAATAGAGCCGCGTACATACCAGGCTGGTAGTGAACGGGAAATTGAAGCAAACCGCCAAGACCT
GAAATTGATGAGGATACTCAGACCCACCTTGGAGGATTTCAGCCAAACAGCAGTCCGGAGGTGCATTGTTGATCA
CAAAGTCCAAAGCCTCCCTGCTGACCAATACCCACCAAGTCAAATCACAGACCTGATGCCACAGTTCATGAG
GATAAGATTATTCTACATGGACAGCACCAGGAGATAATTGATGTTGAAAAGTTCAACGTTATATCATAAGA
ATAAGTGCAGTATTCTGATCTAAGAGACAGTTGATGATGCTCTCAAGTAAATACTACTGATCTGTCACCA
AAGGAGGCCAACTCCAAGGAAAGCTTGCATTAAACCAAGAAAATATCTCAGAAGAAAATGCAACCCACATATT
ATTGCCATTAAAGTATAGATAAAAGCAATTGACATCAAAGTATCCAACATTGCAACAGTAACCTTGTATC
CCTCAAGCAAATCCTGATGACATTGATCCTACACCTACTCCTACTCCTACTGATAAAAGTCATAAT
TCTGGAGTTAATATTCTACGCTGGTATTGCTGTGATTGGGCTGTTGTAATTGTTAACTTTATTAAAGTACC
ACCATTTGAACCTTAACGAAGAAAAAAATCTCAAGTAGACCTAGAAGAGGTTAAAAAAACAAAACATGTAA
GTAAGGATATTCTGAATCTTAAACATTCTGATGTCATCAAACCTGATCAAACATGTTAAGATGTG
GAAAAGGATACTTGTATTAAATAAAAACACTCATGGATATGTAAGGAAACTGTCAGGATTTAAGATGTTCA
TTTATTGTTATTGTAAGAAATAGTGTGATGAAACAAAGATCCTTCTGATCAACTGATACCTGGTTGTTATT
ATTGATGCAACAGTTCTGAATGATATTCAAATTGATCAAGAAATTAAACATCTATCTGAGTAGTCAA
AATACAAGTAAAGGAGAGCAAATAACACATTGGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAA
AAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAG

FIGURE 70

MGLFRGFVFLVLCLLHQSNNTSFIKLNNGFEDIVIVIDPSVPEDEKIEQIEDMVTTASTYL
FEATEKRFKKNVSILIPENWKENPQYKRPKHENKHADIVVAPPTLPGRDEPYTKQFTECGE
KGEYIHFTPDLGGKKQNEYGPPGKLFVHEWAHLRGVFDEYNEDQPFYRAKSKKIEATRCSA
GISGRNRVYKCQGGSCLSACRIDSTTKLYGKDCQFPDKVQTEKASIMFMQSIDSVEFCNE
KTHNQEAPSLQNIKCNFRSTWEVISNSEDFKNTIPMVTPPPPVFSLLKISQRIVCLVLDKSG
SMGGKDRLNRMNQAAKHFLQTVENGSWGMVHFDSTATIVNKLIQIKSSDERNTLMAGLPTY
PLGGTSICSGIKYAFQVIGELHSQDGSEVLLTDGEDNTASSCIDEVKQSGAIVHFIAGRA
ADEAVIEMSKITGGSHFYVSDEAQNNGLIDAFGALTSGNTDLSQKSLQLESKGTLNSNAWMN
DTVIIDSTVGKDTFFLITWNSLPPSISLWDPSGTIMENFTVDATSKMAYLSIPGTAKVGTWAY
NLQAKANPETLTITVTSRAANSSVPPITVNAKMNDVNSFPSPMIVYAEILQGYVPVLGANVT
AFIESQNGHTEVLELLDNGAGADSFKNDGVYSRYFTAYTENGRYSLKVRAGGANTARLKLKP
PLNRAAYIPGWVNNGEIEANPPRPEIDEDTQTTLEDFSRATGGAFVVSQVPSLPLPDQYPPS
QITDLDATVHEDIILTWTAPGDNFVGVQRYIIRISASILDRLDSFDDALQVNTTDLSPKE
ANSKESFAFKPENISEENATHIFIAIKSIDKSNLTSKVSNIAQVTLFIPQANPDDIDPTPTPT
PTPTPDKSHNSGVNISTLVLVIGSVVIVNFILSTTI

Signal peptide:

amino acids 1-21

Putative transmembrane domains:

amino acids 284-300, 617-633

Leucine zipper pattern.

amino acids 469-491, 476-498

N-glycosylation site.

amino acids 20-24, 75-79, 340-344, 504-508, 542-546, 588-592,
628-632, 811-815, 832-836, 837-841, 852-856, 896-900

FIGURE 71

CTCCTTAGGTGGAAACCTGGAGTAGAGTACTGACAGCAAAGACCGGGAAAGACCATACTGCCCCGGGCAGGG
 TGACAAACAGGTGTCATCTTTGATCTCGTGTGGCTGCCCTCTATTCAAGGAAAGACGCCAAGGTAATT
 GACCCAGAGGAGCAATGATGTAGCCACCTCTAACCTCCCTTGAACCCCAAGTATGCCAGGATTACTAG
 AGAGTGTCAACTCAACCAGCAAGCGGCTCCTCGGCTTAACCTGTGGTGGAGGAGAGAACCTTGTGGGCTG
 GTTCTCTTAGCAGTGCCTAGAAGTGAATTGCCTGAGGGTGGACCAGAAGAAAGGAAAGGTCCCTTGTGTTG
 GCTGCACATCAGGAAGGCTGTGATGGAATGAAGGTGAAACTTGGAGATTCACTCAGTCATGCTCTGCCT
 GCAAGATCATCCTTAAAGTAGAGAAGCTGCTCTGTGTTAACTCCAAGAGGCAGAACCTCGTTAGAA
 GGAATGGATGCAAGCAGCTCCGGGGCCCAAACGCATGCTTCTGTGGCTAGGCCAGGGAAAGCCCTCCGTG
 GGGGGCCCGGCTTGAGGGATGCCACCGGTTCTGGACGCATGGCTGATTCTGA**ATG**ATGATGGTTCGCCGGGG
 CTGCTTGCCTGGATTCCCGGGTGGTTTGCTGGTCTCTGCTGTGCTATCTCTGTCCTGACATGTTG
 GCCTGCACCCCAAAGGTGACGAGGAGCAGCTGGCACTGCCAGGGCAACAGCCCCACGGGGAAAGGAGGGTAC
 CAGGCCGTCTCAGGAGTGGGAGGAGCAGCACCGCAACTACGTGAGCAGCCTGAAGGGCAGATGCCACAGCTC
 AAGGAGGAGCTGCAGGAGAGGAGTGGCAGCTCAGGAATGGGAGTACCAAGGCCAGCGATGCTGCTGGG
 CTGGCAGAGGCCCGAGAGAAACCCAGGCCACCTCTGGCCTCTGCACTCGCAAGGTGGACAAGGCAGAG
 GTGAATGCTGGCTCAAGCTGGCACAGAGTATGCAGCAGTGCCTTCGATAGCTTACTCTACAGAAGGTGTAC
 CAGCTGGAGACTGGCTTACCCGCCACCCCGAGGAGAAGCCTGTGAGGAAGGACAAGGGATGAGTGGTGGAA
 GCCATTGAATCAGCCTGGAGACCTGAAACAATCCTGCAGAGAACAGCCCCAATCACGTCCTTACACGGCCTCT
 GATTTCATAGAAGGGATCTACCGAACAGAAAGGGACAAGGGACATTGTATGAGCTCACCTCAAAGGGACCAC
 AAACACGAATTCAAACGGCTCATCTTATTCGACCATTAGCCCCATCATGAAAGTAAAAATGAAAAGCTAAC
 ATGGCCAACACGTTATCAATGTTATCGTGCCTCTAGAAAAAGGTGGACAAGTCCGGCAGTCATGCAAAAT
 TTCAGGGAGATGTGCAATTGAGCAGGATGGGAGGTCCATCTCACTGTTTACTTGGAAAGAAGAAATAAAAT
 GAAGTCAAAGGAATACTGAAAACACTTCCAAAGCTGCCAACTTCAGGAACCTTACCTTATCCAGCTGAATGGA
 GAATTTCTCGGGAAAGGGACTTGTGTTGGAGCCGCTCTGGAAGGGAAAGCAACGTCCTCTCTTTCTGT
 GATGTGGACATCTACTTCACATCTGAATTCTCAATACTGTAAGGCTGAATACACAGCCAGGGAGAAGGTATTT
 TATCCAGTTCTTCAGTCAGTACAATCCTGGCATATAACGGCCACCATGATGCACTCCCTCCCTGGAAACAG
 CAGCTGGCATAAAGAAGGAAACTGGATTTGGAGAGACTTTGGATTGGGATGACGTGTCAGTATCGGTAGAC
 TTCATCAATATAGGTGGGTTGATCTGGACATCAAAGGCTGGGGCGAGAGGATGTGCACCTTATCGCAAGTAT
 CTCCACAGCAACCTCATAGTGGTACGGACGCCGTGCGAGGACTCTCCACCTCTGGCATGAGAACGCGCTGCATG
 GACGAGCTGACCCCCGAGCAGTACAAGATGTGCATGCCAGGCCATGAACAGGCCATCCCCACGGCCAGCTG
 GGCATGCTGGTGTTCAGGCACGAGATAGAGGCTCACCTCGAAACAGAACAGAACAGAACAGTAGCAAAA
TGAACTCCCAGAGAAGGGATTGTGGGAGACACTTTCTTCTTCAATTACTGAAAGTGGCTGCAACAGAGA
 AAAGACTTCCATAAGGAGCACAAGAACATTGGACTGATGGGTCAAGAGATGAGAACAGCTCCGATTCTCTGT
 TGGGCTTTTACAACAGAAATCAAATCTCCGTTGGCTGCAAAAGTAACCCAGTGCACCCCTGTGAAGTGTCT
 GACAAAGGAGAATGCTGTGAGATTATAAGCCTAATGGTGTGGAGGTTTGATGGTGTGTTACAAATACGTGAGA
 CCTGTTTTGTGCTCATTGAAATATTGATTGATTAAAGAGCAGTTGTAAGGAAATTCTATTAGCATGAAAGG
 CAAGCATATTCTCCTCATATGAAATGAGCCTATCAGCAGGGCTCTAGTTCTAGGAATGCTAAATATCAGAAGG
 CAGGAGAGGAGATAGGCTTATTATGATACTAGTGAGTACATTAAGTAAAATGGACCAGAAAAGAAAAGAA
 ACCATAAATATCGTGTATATTCCCCAAGATTAAACAAAATAATCTGCTTATCTTTGGTGTCTTTAA
 CTGTCCTCGTTTTCTTATTAAAGCACTTTCTGCTGAGTTAGTCTGCTTATTTAATTAC
 CACTTGCAAGCCTACAAGAGAGCACAAGTGGCTACATTGTTATTTAAGAAGATACTTGAGATGCA
 TTATGAGAACCTTCAGTCAGCATCAAATTGATGCCATATCCAAGGACATGCCAAATGCTGATTCTGTCAGGC
 ACTGAATGTCAGGCATTGAGACATAGGGAGGAAAGTGGTTGTACTAATACAGACGTACAGATACTTCTGTGAG
 AGTATTTCAGAAGAGGAGCAACTGAACACTGGAGGAAAGAAAATGACACTTCTGCTTACAGAAAAGGAAACT
 CATTCACTGGTGTATCGTGTACCTAAAGTCAGAACCCACATTCTCCTCAGAAGTAGGGACCGCTTT
 CTTACCTGTTAAATAACCAAAGTATACCGTGTGAACCAAACAAATCTCTTCAAAACAGGGTGTCTCCTGG
 CTTCTGGCTTCCATAAGAAGAAATGGAGAAAATATATATATATATATTGTGAAAGATCAATCCATCTG
 CCAGAATCTAGTGGGATGGAAGTTTGCTACATGTTATCCACCCAGGCCAGGTGGAAAGTAACGTGAAATT
 TTAATTAAAGCAGTTCACTCAATCACCAAGATGCTCTGAAAATTGCAATTACCAATTCAAACATTT
 TAAAAATAAAATACAGTTAACATAGAGTGGTTCTCATGTGAAAATTATTAGCCAGCACCAGATGCA
 CTAATTATCTTGTGAGTCCTGCTTGTGCTCACAGTAAACTCATTGTTAAAAGCTTCAAGAACATTC
 GCTGTTGGTGTGTTAAAATGCATTGATTGATTGACTGGTAGTTATGAAATTAAATTAAAACACAGGCCA
 TGAATGGAAGGTGGTATTGACAGCTAATAAAATGATTGTGGATATGAA

72/168

FIGURE 72

MMMVRRGLLAWISRVVVLVLLCCAISVLYMLACTPKGDEEQLALPRANSPTGKEGYQAVLQE
WEEQHRNYVSSLKRQIAQLKEELQERSEQLRNGQYQASDAAGLGLDRSPPEKTQADLLAFLHS
QVDKAEVNAGVKLATEYAAVPFDSFTLQKVYQLETGLTRHPEEKPVRKDKRDELVEAIESALE
TLNNPAENSPNHRPYTASDFIEGIYRTERDKGTLYELTFKGDHKHEFKRLILFRPFSPIMVK
NEKLNMANTLINVIVPLAKRVDKFRQFMQNREMCEQDGRVHLTVVYFGKEEINEVKGILEN
TSKAANFRNFTFIQLNGEFSRGKGLDVGARFWKGSNVLLFFCDVDIYFTSEFLNTCRLNTQPG
KKVFYPVLFQSQYNPGIIYGHDAVPPLEQQLVIKKETGFWRDFGFGMTQCQYRSDFINIGGFDL
DIKGWGGEDVHLYRKYLHSNLIVVRTPVRGFLFHLWHEKRCMDELTPEQYKMCMQSKAMNEASH
GQLGMLVFRHEIEAHLRKQKQKTSSKKT

Important features:

Signal peptide:

amino acids 1-27

N-glycosylation sites.

amino acids 315-319, 324-328

N-myristoylation sites.

amino acids 96-102, 136-142, 212-218, 311-317, 339-345, 393-399

Amidation site.

amino acids 377-381

FIGURE 73

GAGACTGCAGAGGGAGATAAAGAGAGAGGGCAAAGAGGGCAGCAAGAGAGTTGTCTGGGGATC
CAGAAACCCATGATACCTACTGAACACCGAATCCCCTGGAAGGCCACAGAGACAGAGACAGC
AAGAGAAGCAGAGATAAATACACTCACGCCAGGAGCTCGCTCGCTCTCTCTCTCA
CTCCTCCCTCCCTCTCTGCCTGTCCTAGTCCTCTAGTCCTCAAATTCCCAGTCCCTGC
ACCCCTCCCTGGGACACTATGTTGTTCTCCGCCCTCCTGCTGGAGGTGATTGGATCCTGGCT
GCAGATGGGGTCAACACTGGACGTATGAGGGCCACATGGTCAGGACCATTGCCAGCCTCT
TACCCCTGAGTGTGAAACAATGCCAGTCGCCATCGATATTGAGACAGACAGTGTGACATT
GACCCCTGATTTGCCTGCTCTGCAGCCCCACGGATATGACCAGCCTGGCACCGAGCCTTGGAC
CTGCACAAACAATGCCACACAGTGCACACTCTCTGCCCTACCCCTGATCTGGGTGGACTT
CCCCGAAAATATGTAGCTGCCAGCTCCACCTGCACTGGGTGAGAAAGGATCCCCAGGGGG
TCAGAACACCAGATCAACAGTGAAGCCACATTGAGACACTCCACATTGTACATTGACTCT
GATTCTATGACAGCTTGAGTGAGGCTGCTGAGAGGCCTCAGGGCTGGCTGTCTGGCATHC
CTAATTGAGGTGGGTGAGACTAAGAATATAGCTTATGAACACATTCTGAGTCACTTGATGAA
GTCAGGCATAAGATCAGAACCTCAGTGCCTCCCTCAACCTAACAGAGAGCTGCTCCCAA
CAGCTGGGGCAGTACTCCGCTACAATGGCTCGCTCACAACTCCCCCTGCTACCAGAGTGTG
CTCTGGACAGTTTTATAGAAGGTCCCAGATTCAATGAAACAGCTGGAAAAGCTTCAGGGG
ACATTGTTCTCCACAGAACAGAGGAGCCCTCTAACGCTCTGGTACAGAACTACCGAGCCCTCAG
CCTCTCAATCAGCGCATGGCTTGCCTTCAAGCAGGATCCTCGTATACCACAGGT
GAAATGCTGAGTCTAGGTGTAGGAATCTTGGTTGGCTGTCTGCCTCTCCTGGCTGTTAT
TTCATTGCTAGAAAGATTCGGAAGAACAGAGGCTGGAAAAGCGAAAGAGTGTGGTCTTCACCTCA
GCACAAGCCACGACTGAGGCATAAATTCTCTCAGATAACCATGGATGTGGATGACTCCCT
CATGCCTATCAGGAAGCCTCTAAATGGGTGAGGATCTGGCCAGAAACACTGTAGGAGTAG
TAAGCAGATGTCCTCCTCCCTGGACATCTCTAGAGAGGAATGGACCCAGGCTGTCATTCC
AGGAAGAACTGCAGAGCCTCAGCCTCTCAAACATGTAGGAGGAATGAGGAATCGCTGTG
TTGTTAATGCAGAGANCAAACCTCTGTTAGTGCAGGGGAAGTTGGATATACCCAAAGTC
CTCTACCCCTCACTTTATGCCCTTCCCTAGATATACTGCAGGATCTCTCCTTAGGATAA
AGAGTTGCTGTTGAAGTTGTATATTTGATCAATATATTGAAATTAAAGTTCTGACTTT

74/168

FIGURE 74

MLFSALLLEVIWILAADGGQHWTYEGPHGQDHWPASYPECGNNAQSPIDIQTDSVTFPDLPA
LQPHGYDQPGTEPLDLHNNGHTVQLSLPSTLYLGGLPRKYVAAQLHLHWGQKGSPGGSEHQIN
SEATFAELHIVHYDSDSYDSLSEAAERPQGLAVLGILIEVGETKNIAYEHILSHLHEVRHKDQ
KTSVPPFNLRELLPKQLGQYFRYNGSLTTPCYQSVLWTVFYRRSQISMEQLEKLQGTLFSTE
EEPSKLLVQNYRALQPLNQRMVFASFIQAGSSYTTGEMSLGVGILVGCLCLLLAVYFIARKI
RKKRLENRKSVVFTSAQATTEA

Important features of the protein:

Signal peptide:

amino acids 1-15

Transmembrane domain:

amino acids 291-310

N-glycosylation site.

amino acids 213-216

Eukaryotic-type carbonic anhydrases proteins

amino acids 197-245, 104-140, 22-69

75/168

FIGURE 75

TGCCGCTGCCGCCGCTGCTGCTGTTGCTCCTGGCGGCCCTGGGGACGGCAGTCCCTGTG
TCTCTGGTGGTTGCCCTAACACCTGCAAACATCACCTCTTATCCATCAACATGAAGAATGTCC
TACAATGGACTCCACCAGAGGGCTTCAAGGAGTTAAAGTTACACTGTGCAGTATTCA
TCACAAATTGGCCCACCAGAGGTGGCACTGACTACAGATGAGAAGTCCATTCTGTTGCCTG
ACAGCTCCAGAGAAGTGGAAAGAGAAATCCAGAAGACCTCCTGTTCCATGCAACAAATATAC
TCCAATCTGAAGTATAACGTGTCTGTGTTGAATACTAAATCAAACAGAACGTGGTCCCAGTGT
GTGACCAACCACACGCTGGTCTACCTGGCTGGAGCCGAACACTCTTACTGCGTACACGTG
GAGTCCTCGTCCCAGGGCCCCCTGCCGTGCTCAGCCTCTGAGAAGCAGTGTGCCAGGACT
TTGAAAGATCAATCATCAGAGTTCAAGGCTAAATCATCTCTGGTATGTTGCCATATCT
ATTACCGTGTCTTTCTGTGATGGCTATTCCATCTACCGATATATCCACGTTGGCAAA
GAGAAACACCCAGCAAATTGATTGATTTGAAATGAATTGACAAAAGATTCTTGTG
CCTGCTGAAAAAATCGTATTAACTTATCACCCCTCAATATCTGGATGATTCTAAAATTCT
CATCAGGATATGAGTTACTGGAAAAAGCAGTGATGTATCCAGCCTTAATGATCCTCAGCCC
AGCGGGAACCTGAGGCCCTCAGGAGGAAGAGGAGGTGAAACATTAGGTATGCTTCGCAT
TTGATGAAATTGGACTCTGAAGAAAACACGGAAGGTACTTCTCACCCAGCAAGAG
TCCCTCAGCAGAACAAATACCCCGGATAAAACAGTCATTGAATATGAATATGATGTCAGAAC
ACTGACATTGTGGGGCCTGAAGAGCAGGAGCTCAGTTGCAGGAGGAGGTGCCACACAA
GGAACATTATTGGAGTCGCAGGCAGCGTTGGCAGTCTGGGCCGAAACGTTACAGTACTCA
TACACCCCTCAGCTCCAAGACTTAGACCCCTGGCGCAGGAGCACACAGACTCGGAGGAGGG
CCGGAGGAAGGCCATCGACGACCTGGTCAGTGGATCCCCAAACTGGCAGGCTGTGTATT
CCTCGCTGTCCAGCTCGACCAGGATTCAAGAGGGCTGCGAGCCTCTGAGGGGGATGGCTC
GGAGAGGAGGGTCTCTATCTAGACTCTATGAGGAGCCGGCTCCAGACAGGCCACCAGGAGAA
AATGAAACCTATCTCATGCAATTCAAGGAGGATGGGGTTATATGTGCAGATGGAAAACTGA
TGCCAAACACTCCTTTGCCTTGTGCAAACAAAGTGAAGTCACCCCTTGATCCCA
GCCATAAAAGTACCTGGATGAAAGAAGTTTCCAGTTGTCAGTGTCTGTGAGAATTACTT
ATTCTTTCTCTATTCTCATAGCACGTGTGATTGGTTCATGCATGTAGGTCTCTAACAA
TGATGGTGGGCCTCTGGAGTCCAGGGGCTGGCCGGTTGTTCTATGCAGAGAAAGCAGTCAATA
AATGTTGCCAGACTGGTGCAGAATTATTCAAGGTGGGTGT

76/168

FIGURE 76

MSYNGLHQRFKELKLLTLCISISSQIGPPEVALTTDEKSISVVLTAPEKWKRNPEDLPVSMQQ
IYSNLKYNVSVLNTKSNRTWSQCVTNHTLVLTWLEPNTLYCVHVESFVPGPPRRAQPSEKQCA
RTLKDQSSEFKAKIIFWYVLPISITVFLFSVMGYSIYRYIHVGKEKHPANLILIGNEFDKRF
FVPAEKIVINFITLNISDDSKISHQDMSLLGKSSDVSSLNDPQPSGNLRPPQEEEVKGHLGYA
SHLMEIFCDSEENTEGTSLTQQESLSRTIPPDKTVIEYEYDVRTTDICAGPEEQELSLOEEVS
TQGTLLESQAALAVLGPQTLQYSYTPQLQDLDPLAQEHTDSEEGPEEEPSTTLVDWDPQTGRL
CIPSLSSFDQDSEGCEPSEGDGGLGEEGLLSRLYEEPAPDRPPGENETYLMQFMEEWGLYVQMN

Important features:

Signal peptide:

amino acids 1-28

Transmembrane domain:

amino acids 140-163

N-glycosylation sites.

amino acids 71-74, 80-83, 89-92, 204-207, 423-426

77/168

FIGURE 77

GAGGAGCGGGCGAGGACTCCAGCGTCCCAGGTCTGGCATCCTGCACTTGCTGCCCTCTGAC
ACCTGGGAAGATGGCCGGCCCGTGGACCTCACCCCTCTGTGGTTGCTGGCAGCCACCTT
GATCCAAGCCACCCTCAGTCCCAGTGCAGTTCTCATCCTCGGCCAAAAGTCATCAAAGAAAA
GCTGACACAGGAGCTGAAGGACCACAACGCCACCAGCATCCTGCAGCAGCTGCCGTGCTCAG
TGCCATGCGGAAAAGCCAGCCGGAGGCATCCCTGTGCTGGCAGCCTGGTAACACCGTCCT
GAAGCACATCATCTGGCTGAAGGTCACTCACAGCTAACATCCTCAGCTGCAGGTGAAGCCCTC
GCCAATGACCAGGAGCTGCTAGTCAAGATCCCCCTGGACATGGTGGCTGGATTCAACACGCC
CCTGGTCAAGACCATCGTGGAGTTCCACATGACGACTGAGGCCAAGGCCACCATCCGCATGGA
CACCAAGTGCAAGTGGCCCCACCCGCTGGTCCTCAGTGACTGTGCCACCAGCCATGGGAGCCT
GCGCATCCAAGTGTATAAGCTCTCCTCCTGGTAACGCCCTAGCTAACAGGTCACTGAA
CCTCCTAGTGCATCCCTGCCAATCTAGTAAAAACAGCTGTGTCCCCTGATCGAGGCTTC
CTTCAATGGCATGTATGCAGACCTCCTGCAGCTGGTAAGGTGCCATTCCCTCAGCATTGA
CCGTCGGAGTTGACCTCTGTATCCTGCCATCAAGGGTGACACCATTAGCTCTACCTGGG
GCCAAGTTGGACTCACAGGAAAGGTGACCAAGTGGTCAATAACTCTGCAGCTCCCT
GACAATGCCACCCTGGACAACATCCGTTAGCCTCATCGTGAGTCAGGACGTGGTAAAGC
TGCAGTGGCTGCTGTCTCTCCAGAAGAATTCACTGGCCTGTTGGACTCTGTGCTTCTGA
GAGTGCCCATGGCTGAAGTCAAGCATGGCTGATCAATGAAAAGGCTGCAGATAAGCTGGG
ATCTACCCAGATCGTGAAGATCTAACACTCAGGACACTCCGAGTTTATAGACCAAGGCCA
TGCCAAGGTGGCCCAACTGATCGTGTGGAAAGTGTTCCTCCAGTGAAGCCCTCCGCCCTT
GTTCACCCCTGGGATCGAAGCCAGCTCGGAAGCTCAGTTACACCAAGGTGACCAACTTAT
ACTCAACTGAATAACATCAGCTCTGATCGGATCCAGCTGATGAACCTCTGGATTGGCTGGTT
CCAACCTGATGTTCTGAAAAACATCATCACTGAGATCATCCACTCCATCCTGCTGCCGAACCA
GAATGGCAAATTAGATCTGGGTCCCAGTGTCACTGGTAAGGCCTGGGATTGAGGCAGC
TGAGTCCTCACTGACCAAGGATGCCCTGTGCTTACTCCAGCCTCTGTGGAAACCCAGCTC
TCCTGTCTCCAGTGAAGACTTGGATGGCAGCCATCAGGAAGGCTGGTCCCAGCTGGAGT
ATGGGTGTGAGCTATAGACCATCCCTCTGCAATCAATAAACACTTGCTGTGAAAAA

78/168

FIGURE 78

MAGPWTFTLLCGLLAATLIQATLSPTAVLILGPKVIKEKLTQELKDHNATSILQQLPLLSAMR
EKPAGGI PVLGSLVNTVLKHIIWLKVITANILQLOVKPSANDQELLVKIPLDMVAGFNTPLVK
TIVEFHMTTEAQATIRMDTSASGPTRLVLSDCATSHGSLRIQLLYKLSFLVNALAKQVMNLLV
PSLPNLVKNQLCPVIEASFNGMYADLLQLVKVPISLSIDRLEFDLLYPAIKGDTIQLYLGAKL
LDSQGKVTKWFNNSAASLTMP TL DNI PFSLIVSQDVVKAAVAAVLSPEEFMVLLDSVLPEAH
RLKSSIGLINEKAADKLGSTQIVKILTQDTPEFFIDQGHAKVAQLIVLEVFPSSEALRPLFTL
GIEASSEAQFYTKGDQLILNLNNISSLRQLMNSGIGWFQPDVLKNIITEIIHSILLPNQNGK
LRSGVPVSLVKALGFEAAESSLTKDALVLTPASLWKPSGPVSQ

Important features of the protein:

Signal peptide:

amino acids 1-21

N-glycosylation sites.

amino acids 48-51, 264-267, 401-404

Glycosaminoglycan attachment site.

amino acids 412-415

LBP / BPI / CETP family proteins.

amino acids 407-457

FIGURE 79

GAGAGAAGTCAGCCTGGCAGAGAGACTCTGAAATGAGGGATTAGAGGTGTTCAAGGAGCAAGA
GCTTCAGCCTGAAGACAAGGGAGCAGTCCCTGAAGACGCTTCTACTGAGAGGTCTGCC**ATGGC**
CTCTCTTGGCCTCCAACTTGTGGCTACATCCTAGGCCTTCTGGGGCTTTGGGCACACTGGT
TGCCATGCTGCTCCCCAGCTGGAAAACAAGTTCTTATGTCGGTGCAGCATTGTGACAGCAGT
TGGCTTCTCCAAGGGCTCTGGATGGAATGTGCCACACACAGCACAGGCATCACCCAGTGTGA
CATCTATAGCACCCCTCTGGGCCTGCCGCTGACATCCAGGCTGCCAGGCCATGATGGTGAC
ATCCAGTGCAATCTCCTCCCTGGCCTGCATTATCTGTGGTGGCATGAGATGCACAGTCTT
CTGCCAGGAATCCCGAGCAAAGACAGAGTGGCGGTAGCAGGTGGAGTCTTTCATCCTTGG
AGGCCTCCTGGGATTCAATTCTGTTGCCTGGAATCTCATGGGATCCTACGGACTTCTACTC
ACCACTGGTGCCTGACAGCATGAAATTGAGATTGGAGAGGCTTTACTTGGCATTATTC
TTCCCTGTTCTCCCTGATAGCTGGAATCATCCTCTGCTTTCTGCTCATCCCAGAGAAATCG
CTCCAACTAACGATGCCTACCAAGCCAACCTCTGCCACAAGGAGCTCTCCAAGGCCTGG
TCAACCTCCAAAGTCAAGAGTGAGTTCAATTCTACAGCCTGACAGGGTATGTG**TGA**AGAAC
CAGGGGCCAGAGCTGGGGGTGGCTGGTCTGTGAAAAACAGTGGACAGCACCCGAGGGCCA
CAGGTGAGGGACACTACCACTGGATCGTGTAGAAGGTGCTGCTGAGGATAGACTGACTTGG
CCATTGGATTGAGCAAAGGCAGAAATGGGGCTAGTGTAAACAGCATGCAGGTTGAATTGCCAA
GGATGCTGCCATGCCAGCCTTCTGTTCTCACCTGCTGCTCCCTGCCCTAAGTCCCC
AACCTCAACTTGAAACCCATTCCCTTAAGCCAGGACTCAGAGGATCCCTTGCCCTGCTGGT
TTACCTGGGACTCCATCCCCAAACCCACTAATCACATCCCAGTGAACCTGACTGACCCCTGTGATCAA
AGACCCTCTCTGGCTGAGGTTGGCTTAGCTATTGCTGGGATGGGAAGGGAGAACAGT
GGCTTTGTGGCATTGCTCTAACCTACTTCTCAAGCTCCCTCAAAGAAACTGATTGGCCC
TGGAACCTCCATCCACTCTGTTATGACTCCACAGTGTCCAGACTAATTGTGATGAAC
AAATAAAACCATCCTACGGTATCCAGGGAACAGAAAGCAGGATGCAGGATGGGAGGACAGGAA
GGCAGCCTGGACATTAAAAAAATA

80/168

FIGURE 80

MASLGLQLVGYILGLLGLLGTLVAMLLPSWKTSSYVGASIVTAVGFSKGLWMECATHSTGITO
CDIYSTLLGLPADIQAAQAMMVTSSTAISSLACIISVVGMRCTVFCQESRAKDRVAVAGGVFFI
LGGLLGFIIPVAWNLHGILRDFYSPLVPSMKEIGEALYLGIISSLFSLIAGIILCFSCSSQR
NRSNYYDAYQAQPLATRSSPRPGQPPKVKSEFNSYSLTGYV

Important features of the protein:

Signal peptide:

amino acids 1-24

Transmembrane domains:

amino acids 82-102, 117-140, 163-182

N-glycosylation site.

amino acids 190-193

PMP-22 / EMP / MP20 family proteins.

amino acids 46-59

FIGURE 81

CCACACGCGTCCGCGCCTCTCCCTTGCTGGACCTTCCTCGTCTCTCCATCTCTCCCTCCTT
TCCCCCGCGTTCTCTTCCACCTTCTCTTCTCCACCTAGACCTCCCTGCCCTCCT
TCCTGCCCAACCGCTGCTTCCTGGCCCTCTCCGACCCCGCTCTAGCAGCAGACCTCCTGGGGT
CTGTGGGTTGATCTGTGGCCCTGTGCCTCCGTGTCCTTCTCCCTCCCTCCGACTCC
GCTCCCGGACCAAGCGGCCTGACCTGGGGAAAGGATGGTCTCCGAGGTGAGGGTCTCTCC
CTTGCTGGACTCGCGCTGCTCTGGTTCCCCCTGGACTCCCACGCTCGAGGCCAGACAT
GTTCTGCCTTTCCATGGGAAGAGATACTCCCCCGGGAGAGCTGGCACCCCTACTTGGAGCC
ACAAGGCCTGATGTACTGCCTGCGCTGTACCTGCTCAGAGGGCGCCATGTGAGTTTACCG
CCTCCACTGTCCGCTGTCCACTGCCCGACGCTGTGACGGAGCCACAGCAATGCTGTCCAA
GTGTGTGGAACCTCACACTCCCTGGACTCCGGGCCCCACCAAAGTCTGCCAGCACACGG
GACCATGTACCAACACGGAGAGATCTCAGTGCCTGAGCTGTTCCCTCCGCCCTGCC
CCAGTGTGCTCTGCAGCTGCACAGAGGGCCAGATCTACTGCCCTGACAAACCTGCC
ACCAGGCTGCCAGCACCCCTCCACTGCCAGACTCCTGCTGCCAGCCTGCAAAGATGAGGC
AAAGTGAAGCAATCGGATGAAGAGGACAGTGTGCAGTCGCTCCATGGGTGAGACATCCTCAGGA
TCCATGTTCCAGTGATGCTGGAGAAAGAGAGGGCCGGCACCCAGCCCCACTGCCCTCAG
CGCCCTCTGAGCTCATCCCTGCCACTTCAGACCCAAGGGAGCAGGCAGCACA
GATCGCCTGAAGGAGAACATAAGAAAGCCTGTGCATGGCGGGAAAGACGTACTCC
GGAGGTGTGGCACCCGGCTTCCGTGCCTCGGCCCTTGCCCTGCATCCTATGCACCTGTGA
GGATGGCCGCCAGGACTGCCAGCGTGTGACCTGTCCACCGAGTACCCCTGCCGT
GAAAGTGGCTGGGAAGTGCTGCAAGATTGCCAGAGGACAAAGCAGACCC
GATCAGTTCTACCAGGTGTCCAAGGCACCGGGCGGGTCTCGTCCACACATCGGT
AAGCCCAGACAACCTCGCTCGCTTGCCCTGGAACACGAGGCCTCG
GACTCAAGAAAGTCAGGAAGCAAGACTCCAG
GCCACACAGCCAGAACATCTCCACTTGACTCAGATCAAGAAAGTCAGGAAGCAAGACTCC
AAGAGGCACAGCACTCCGACTGCTCGCTGGCCCCACGAAGGT
CCCAGACCC
CTGGAGCTGAAGGT
CACGGCCAGACAAAGTGACCAAGACATAACAAAGAC
CTAA
CAGTTGCAGATATGAGCTGTATAATTGTTATTATATTAATAATAAAGAAGTTGC
ATTACCCCTCAAAAAAAAAAAAAAAA

82/168

FIGURE 82

MVPEVRVLSSLLGLALLWFPLDSHARARPDMFCLFHGKRYSPGESWHPYLEPQGLMYCLRCTC
SEGAHVSCYRLHCPPVHCPQPVTEPQQCCPKCVEPHTPSGLAPPKSCQHNGTMYQHGEIFSA
HELPSPRLPNQCVLCSCTEGQIYGLTTCPPEPGCPAPLPLPDSCCQACKDEASEQSDEEDSVQ
SLHGVRHPQDPCSSDAGRKRGPGTPAPTGLSAPLSFIPRHFRPKGAGSTTVKIVLKEHKKAC
VHGGKTYSHGEVWHPAFRAFGPLPCILCTCEDGRQDCQRVTCPTEYPCRHPEKVAGKCCKICP
EDKADPGHSEISSTRCPKAPGRVLVHTSVSPSPDNLRRFALEHEASDLVEIYLWKLVKDEETE
AQRGEVPGPRPHSQNLPLSDQESQEARLPERGTALPTARWPPRRSLERLPSPDGAEGHGQS
RQSDQDITKT

Signal peptide:

amino acids 1-25

FIGURE 83

GACAGCTGTGTCTCGATGGAGTAGACTCTCAGAACAGCGCAGTTGCCCTCGCTCACGCAGA
GCCTCTCCGTGGCTCCGCACCTGAGCATTAGGCCAGTTCTCCTCTCTCTAATCCATCC
GTCACCTCTCCTGTCAATCCGTTCCATGCCGTGAGGTCCATTACAGAACACATCC **ATGGCTC**
TCATGCTCAGTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGGCAGTGGCAGGTGTTGGC
CAGACAAGCCTGTCCAGGCCTTGGTGGGGAGGACGCAGCATTCTCCTGTTCTGTCTCCTA
AGACCAATGCAGAGGCCATGGAAGTGCAGTTCTCAGGGGCCAGTTCTAGCGTGGTCCACC
TCTACAGGGACGGGAAGGACCAGCCATTTATGCAGATGCCACAGTATCAAGGCAGGACAAAAC
TGGTGAAGGATTCTATTGCGGAGGGCGCATCTCTGAGGCTGGAAAACATTACTGTGTTGG
ATGCTGGCCTCTATGGGTGCAGGATTAGTTCCCAGTCTTACTACCAGAAGGCCATCTGGGAGC
TACAGGTGTCAGCACTGGGCTCAGTTCTCTCATTTCCATCACGGATATGTTGATAGAGACA
TCCAGCTACTCTGTCACTCCTCGGGCTGGTCCCCCGGCCACAGCGAAGTGGAAAGGTCCAC
AAGGACAGGATTGTCCACAGACTCCAGGACAAACAGAGACATGCATGGCCTGTTGATGTGG
AGATCTCTGACCGTCCAAGAGAACGCCGGAGCATATCCTGTTCCATGCCATGCTCATC
TGAGCCGAGAGGTGGAATCCAGGGTACAGATAGGAGATACCTTTGAGCCTATATCGTGGC
ACCTGGCTACCAAAGTACTGGGAATACTCTGCTGTGGCCTATTTTGGCATTGTTGGACTGA
AGATTTCTCTCCAAATTCCAGTGGAAAATCCAGGCCGAATGGACTGGAGAAGAAAGCAG
GACAGGCAGAATTGAGAGACGCCGGAAACACGCAGTGGAGGTGACTCTGGATCCAGAGACGG
CTCACCCGAAGCTCTGCGTTCTGATCTGAAAATGTAACCCATAGAAAAGCTCCCCAGGAGG
TGCCTCACTCTGAGAAGAGATTACAAGGAAGAGTGTGGTGGCTCTCAGAGTTCCAAGCAG
GGAAACATTACTGGGAGGTGGACGGAGGACACAATAAAAGGTGGCGGTGGAGTGTGCCGG
ATGATGTGGACAGGAGGAAGGAGTACGTGACTTGTCTCCGATCATGGTACTGGGTCTCA
GACTGAATGGAGAACATTGTATTCACATTAATCCCGTTTATCAGCGTCTCCCCAGGA
CCCCACCTACAAAATAGGGTCTCCTGGACTATGAGTGTGGACCATCTCCTCTCAACA
TAAATGACCAGTCCCTATTTACCCCTGACATGTCGGTTGAAGGCTTATTGAGGCCCTACA
TTGAGTATCCGTCCTATAATGAGCAAATGGAACCTCCATAGTCATCTGCCAGTCACCCAGG
AATCAGAGAAAGAGGCCCTTGGCAAAGGGCCTCTGCAATCCCAGAGACAAGCAACAGTGGT
CCTCCTCACAGGCAACCACGCCCTCCTCCCCAGGGTGAATG **TAGGATGAATCACATCCCA**
CATTCTCTTAGGGATATTAAGGTCTCTCCTCCAGATCCAAAGTCCCGCAGCAGCCGGCAA
GGTGGCTTCCAGATGAAGGGGACTGGCCTGTCCACATGGGAGTCAGGTGTCATGGCTGCCCT
GAGCTGGGAGGGAAAGAAGGCTGACATTACATTAGTTGCTCTCACTCCATCTGGCTAAGTGA
TCTTGAAATACCACCTCTCAGGTGAAGAACCGTCAGGAATTCCCATCTCACAGGCTGTGGT
AGATTAAGTAGACAAGGAATGTGAATAATGCTTAGATCTTATTGATGACAGAGTGTATCCTAA
TGGTTGTTCAATTACACTTCAAGTAAAAAAA

84/168

FIGURE 84

MALMLSLVLSLLKLGSQWQVFGPDKPVQALVGEDAAFSCFLSPKTNAEAMEVRFFRGQFSSV
VHLYRDGKDQPFMQMPQYQGRTKLVKDSIAEGRISLRLENITVLDAGLYGCRISSQSYQKAI
WELQVSALGSVPLISITGYVDRDIQLLCQSSGFPRPTAKWKGPGQGQDLSTDRTNRDMHGLF
DVEISLTQENAGSISCSMRHAHLSREVESRVQIGDTFFEPISWHLATKVLGILCCGLFFGIV
GLKIFFSKFQWKIQAELDWRRKHGQAEELRDARKHAVEVTLDPETAHPKLCVSDLKTVTHRKAP
QEVPHSEKRFTRKSVVASQSFQAGKHYWEVGGHNKRWRVGVCRDDVDRRKEYVTLSPDHGYW
VLRLNGEHLYFTLNPRFISVFPRTPPTKIGVFLEDYECGTISFFNINDQSLIYTLTCRFEGLLR
PYIEYPSYNEQNGTPIVICPVTQESEKEASWQASAIPETSNSESSSQATTPFLPRGEM

Signal peptide:

amino acids 1-17

Transmembrane domain:

amino acids 239-255

FIGURE 85

AACAGACGTTCCCTCGCGGCCCTGGCACCTTAACCCCAGACATGCTGCTGCTGCTGCC
CTGCTCTGGGGGAGGGAGAGGGCGGAAGGACAGACAAGTAAACTGCTGACGATGCAGAGTTCC
GTGACGGTGCAGGAAGGCCTGTGTCCATGTGCCCTGCTCCTCTACCCCTGCATGGC
TGGATTACCCCTGGCCCAGTAGTCATGGCTACTGGTCCGGGAAGGGCCAATACAGACCAG
GATGCTCCAGTGGCCACAAACAACCCAGCTGGCAGTGTGGAGGAGACTCGGGACCGATT
CACCTCCTGGGGACCCACATACCAAGAATTGCACCCCTGAGCATCAGAGATGCCAGAAGAAGT
GATGCGGGGAGATACTTCTTCGTATGGAGAAAGGAAGTATAAAATGAAATTATAAACATCAC
CGGCTCTGTGAATGTGACAGCCTGACCCACAGGCCAACATCCTCATCCCAGGCACCC
GAGTCCGGCTGCCCTGGAGATCTGACCTGCTGTGCCCTGGCCTGTGAGCAGGGACACCC
CCTATGATCTCCTGGATAGGGACCTCCGTGTCCCCCTGGACCCCTCCACCACCGCTCCTCG
GTGCTCACCCATCCCACAGCCCCAGGACCATGGCACCAGCCTCACCTGTCAGGTGACCTTC
CCTGGGCCAGCGTGACCACGAACAAGACCGTCCATCTCAACGTGTCCTACCCGCTCAGAAC
TTGACCATGACTGTCTCCAAGGAGACGGCACAGTATCCACAGTCTTGGAAATGGCTCATCT
CTGTCACTCCCAGAGGCCAGTCTGCGCCTGGTCTGTGAGTTGATGCAGTGACAGCAAT
CCCCCTGCCAGGCTGAGCCTGAGCTGGAGAGGCCGTGACCTGTGCCCTCACAGCCCTCAAAC
CCGGGGGTGCTGGAGCTGCCCTGGGTGACCTGAGGATGCACTGAAATTACCTGCAGAGCT
CAGAACCTCTGGCTCTCAGCAGGTCTACCTGAACGTCTCCCTGCAGAGCAAAGCCACATCA
GGAGTGACTCAGGGGGTGGTCGGGGAGCTGGAGCCACAGCCCTGGTCTCCTGTCTTC
GTCATCTCGTTGAGGTCTGCAGGAAGAAATCGGCAAGGCCAGCAGCGGGCTGGGA
GATACGGGCATAGAGGATGCAAACGCTGTCAGGGTTCAGCCTCTCAGGGGCCCTGACTGAA
CCTTGGGCAGAAGACAGTCCCCAGACCAGCCTCCCCAGCTCTGCCGCTCCTCAGTGGGG
GAAGGAGAGCTCCAGTATGCATCCCTCAGCTCCAGATGGTGAAGCCTGGACTCGCGGGGA
CAGGAGGCCACTGACACCGAGTACTCGGAGATCAAGATCCACAGATGAAAACTGCAGAGACT
CACCCCTGATTGAGGGATCACAGCCCTCCAGGCAAGGGAGAAGTCAGAGGCTGATTCTGTAG
AATTAACAGCCCTAACGTGATGAGCTATGATAACACTATGAATTATGTGAGAGTAAAAAGC
ACACAGGCTTAGAGTCAAAGTATCTAAACCTGAATCCACACTGTGCCCTCCCTTTATTTT
TTTAACAAAAGACAGACAAATTCTA

86/168

FIGURE 86

MLLLLLPLLWGRERAEGQTSKLLTMQSSVTQEGLCVHVPSCFSYPSHGWIYPGPVVHGYWFR
EGANTDQDAPVATNNPARAVWEETRDRFHLLGDPHTKNCTLISRARRSDAGRYFFRMEKGSI
KWNYKHHRLSVNVTALTHRPNILIPGTLESGCPQNLTCSPWACEQGTPPMISWIGTSVSPLD
PSTTRSSVLTLPQPQDHGTSLTCQVTFPGASVTTNKTVHLNVSYPQNLTMVFQGDGTVST
VLGNNGSSLSLPEGQSLRLVCAVDAVDSNPPARLSLSWRGLTLCPSQPSNPGVLELPWVHLRDA
AEFTCRAQNPLGSQQVYLNVSILQSKATSGVTQGVVGGAGATALVFLSFCVIFVVVRSCRKKSA
RPAAGVGDTGIEDANAVRGASQGPLTEPWAEDSPPDQPPPASARSSVGEHELQYASLSFQMV
KPWDSRGQEATDTEYSEIKIHR

Signal peptide:

amino acids 1-15

Transmembrane domain:

amino acids 351-370

FIGURE 87

AGAAAGCTGCACTCTGTTGAGCTCCAGGGCGCAGTGGAGGGAGGTGAAGGAGCTCTGT
ACCCAAGGAAAGTGCAGCTGAGACTCAGACAAGATTACAATGAACCAACTCAGCTTCCTGCTG
TTTCTCATAGCGACCACCAGAGGATGGAGTACAGATGAGGCTAATACTTACTCAAGGAATGG
ACCTGTTCTCGTCTCCATCTCTGCCAGAAGCTGCAAGGAAATCAAAGACGAATGTCCTAGT
GCATTTGATGGCCTGTATTTCTCCGCACTGAGAATGGTGTATCTACCAGACCTCTGTGAC
ATGACCTCTGGGGTGGCGGCTGGACCCTGGTGGCCAGCGTGCATGAGAATGACATGCGTGGG
AAGTGCACGGTGGCGATCGCTGGTCCAGTCAGCAGGGCAGCAAAGCAGACTACCCAGAGGGG
GACGGCAACTGGGCCAACTACAACACCTTGGATCTGCAGAGGCAGCCACGAGCGATGACTAC
AAGAACCCCTGGCTACTACGACATCCAGGCCAAGGACCTGGCATCTGGCACGTGCCAATAAG
TCCCCCATGCAGCACTGGAGAAACAGCTCCCTGCTGAGGTACCGCACGGACACTGGCTTCCTC
CAGACACTGGACATAATCTGTTGGCATCTACCAGAAATATCCAGTGAATATGGAGAAGGA
AAGTGTGACTGACAACGGCCGGTATCCCTGTGGTCTATGATTTGGCAGGCCAGAAA
ACAGCATCTTATTACTCACCCATGCCAGCGGAATTCACTGCAGGGATTTGTTAGTCAG
GTATTTAATAACGAGAGAGCAGCCAACGCCCTGTGTGCTGGAATGAGGGTCACCGGATGTAAC
ACTGAGCATCACTGCATTGGTGGAGGAGGATACTTCCAGAGGCCAGTCCCCAGCAGTGTGGA
GATTTTCTGGTTTGATTGGAGTGGATATGGAACATCATGTTGGTTACAGCAGCAGCCGTGAG
ATAACTGAGGCAGCTGTGCTTCTATTCTATCGTTGAGAGTTTGTGGAGGGAACCCAGACCT
CTCCTCCCAACCATGAGATCCAAGGATGGAGAACAACTTACCCAGTAGCTAGAATGTTAATG
GCAGAAGAGAAAACAATAATCATATTGACTCAAGAAAAAA

88/168

FIGURE 88

MNQLSFLLFLIATTRGWSTDEANTYFKEWTCSSSPSLPRSCKEIKDECPSAFDGLYFLRTENG
VIYQTFCDMTSGGGGWTLVASVHENDMRGKCTVGDRSSQQGSKADYPEGDGNWANYNTFGSA
EAATSDDYKNPGYYDIQAKDLGIWHVPNKSPMQHWRNSSLRYRTDTGFLQTLGHNLFGIYQK
YPVKYGEKGKWTDNGPVI PVVYDFGDAQKTASYYSPYQREFTAGFVQFRVFNNERAANALCA
GMRVTGCNTEHHCIGGGGYFPEASPQQCGDFSGFDWSGYGTHVGYSSSREITEAAVLLFYR

Important features:

Signal peptide:

amino acids 1-16

N-glycosylation site.

amino acids 163-167

Glycosaminoglycan attachment sites.

amino acids 74-78, 289-293

N-myristoylation sites.

amino acids 76-82, 115-121, 124-130, 253-259, 292-298

89/168

FIGURE 89

CTAGATTGTCGGCTTGCAGGGAGACTTCAGGAGTCGCTGTCTCTGAACCTCCAGCCTCAGAG
ACCGCCGCCCTTGTCCCCGAGGGCCATGGGCCGGGTCTCAGGGCTTGTGCCCTCTCGCTTCCT
GACGCTCCTGGCGATCTGGTGGTCGTACACCTTATTCTGGTCCCGGGACAGCAACATACA
GGCCTGCCTGCCTCTCACGTTACCCCCGAGGGAGTATGACAAGCAGGACATTAGCTGGTGGC
CGCGCTCTGTACCCCTGGGCCTTTGCAGTGGAGCTGGCCGGTTCCCTCTCAGGAGTCTC
CATGTTAACAGCACCCAGAGCCTCATCTCCATTGGGGCTACTGTAGTGCATCCGTGGCCCT
GTCCTTCTTCATATTGAGCGTTGGGAGTGCACTAGCTATTGGTACATTGTCTGCAG
TGCCCTTCCAGCTGTCACTGAAATGGCTTATTGTCACCGTCTTGGGCTGAAAAAGAAACC
CTTCTGATTACCTTCATGACGGGAACCTAACGGACGAAGCCTACAGGGCAAGGGCCGCTTCGT
ATTCCCTGGAAGAAGGAAGGCATAGGCTTCGGTTTCCCTCGAAACTGCTTCTGCTGGAGGA
TATGTGTTGGAATAATTACGTCTTGAGTCTGGATTATCCGCATTGTATTTAGTGCTTGTAA
TAAAATATGTTTAGTAACATTAAGACTTATACAGTTAGGGACAATTAAAAAAA
AAA

90/168

FIGURE 90

MGRVSGLVPSRFLTLLAHLVVVITLFWSRDSNIQACLPLTFTPEEYDKQDIQLVAALSVTLGL
FAVELAGFLSGVSMFNSTQSLISIGAHCASVALSFFIFERWECTTYWYIFVFC SALPAVTEM
ALFVTVFGLKKKPF

Transmembrane domain:

amino acids 12-28 (type II), 51-66, 107-124

FIGURE 91

CTGGGACCCGAAAAGAGAAGGGGAGAGCGAGGGGACGAGAGCGGAGGAAGAAG**ATG**CAACTG
ACTCGCTGCTGTTCTGGTAGCCTCTATCTGGTCATCTGTGGCCAGGAT
GATGGTCCTCCCGGCTCAGAGGACCTGAGCGTGATGACCACGAGGGCAGCCCCGGCCCCGG
GTGCCTCGGAAGCGGGGCCACATCTCACCTAACGCCCCATGGCCAATTCCACTCTCCTA
GGGCTGCTGGCCCCGCTGGGGAGGCTGGGCATTCTGGCAGCCCCAACGCCAAC
CACAGCCCCCACCCCTCAGCCAAGGTGAAGAAAATCTTGGCTGGGCGACTTCTACTCCAAC
ATCAAGACGGTGGCCCTGAACCTGCTCGTCACAGGGAAAGATTGTGGACCATGGCAATGGGACC
TTCAGCGTCCACTTCCAACACAATGCCACAGGCCAGGGAAACATCTCCATCAGCCTCGTGC
CCCAGTAAAGCTGTAGAGTCCACCAGGAACAGCAGATCTCATCGAAGCCAAGGCCTCCAAA
ATCTTCAACTGCCGGATGGAGTGGAGAAGGTAGAACGGGCCGGACCTCGCTTGACC
CACGACCCAGCCAAGATCTGCTCCGAGACCACGCTCAGAGCTCAGCACCTGGAGCTGCTCC
CAGCCCTCAAAGTCGTCGTCTACATCGCCTTACAGCACGGACTATCGGCTGGTCCAG
AAGGTGTGCCAGATTACAACCTACCATAGTGTACCCCCACTACCCATCTGGG**TGA**CCCGGG
GCAGGCCACAGAGGCCAGGGCTGGAGGACAGGCCATGCAGGAGACCATCTGG
ACACCGGGCAGGGAAAGGGTTGGGCCTCAGGCAGGGAGGGGGTGGAGACGAGGAGATGCCAA
GTGGGGCCAGGGCCAAGTCTCAAGTGGCAGAGAAAGGGTCCAAGTGCTGGTCCAACCTGAA
GCTGTGGAGTGAATCACAGGAGCACTGGAGGAGGTGGCTCTGTGCAGCCTCACA
GGGCTTGCCACGGAGCCACAGAGAGATGCTGGTCCCCGAGGCCATGTGGCAGGCCGATCAG
TGTGGCCCAAGATCAAGTCATGGAGGAAGCTAACGCCCCTTGGTCTTGCCATCCTGAGGAAAG
ATAGCAACAGGGAGGGGAGATTCATCAGTGTGGACAGCCTGTCAACTTAGGATGGATGGCT
GAGAGGGCTTCCTAGGAGCCAGTCAGCAGGGTGGGAGGCCAGAGGAGCTCCAGGCC
CCTAGTGGCGCCCTGAGCCCCTTGTCGTGCTGAGCATGGCATGAGGCTGAAGTGGCAACC
CTGGGGTCTTGATGTCTTGACAGATTGACCATCTGTCTCCAGCCAGGCCACCCCTTCCAAA
ATTCCCTCTGCCAGTACTCCCCCTGTACCAACCCATTGCTGATGGCACACCCATCCTTAAG
CTAACAGGACGATTGTGGCCTCCCACACTAACGCCACAGCCCACCGCTGCTGTGTC
CCTCTCCACCCCAACCCCTGCTGGCTCCTCTGGAGCATCCATGTCCGGAGAGGGTCCCT
CAACAGTCAGCCTCACCTGTCAGACCGGGTTCTCCGGATCTGGATGGCGCCGCCCTCAG
CAGCGGGCACGGGTGGGGCGGGGCCAGAGCATGTGCTGGATCTGTTCTGTGTCT
GTCTGTGGGTGGGGGAGGGAGGGAAAGTCTGTGAAACCGCTGATTGCTGACTTTGTGTGA
AGAATCGTGTCTGGAGCAGGAAATAAGCTGCCCGGGCA

92/168

FIGURE 92

MQLTRCCFVFLVQGSLYLVICGQDDGPPGSEDPERDDHEGQPRPRVPRKRGHISPKS RPMANS
TLLGLLAPPGEAWGILGQPPNRPNHSPPPSAKVKKIFGWGDFYSNIKTVALNLLVTGKIVDHG
NGTFSVHFQHNATGQGNISISLVPPSKAVEFHQEQQIFIEAKASKIFNCRM EWEKVERGRRTS
LCTHDPAKICSRDHAQSSATWSCSQPKVVCVYIAFYSTDYRLVQKVC PDNYHSDTPYYPSG

Important features of the protein:

Signal peptide:

amino acids 1-14

N-glycosylation sites.

amino acids 62-65, 127-130, 137-140, 143-146

2-oxo acid dehydrogenases acyltransferase

amino acids 61-71

93/168

FIGURE 93

CGGTGGCCATGACTGCGGCCGTGTTCTCGGCTGCGCCTTCATTGCCTCGGGCCTGCGCTCG
CCCTTTATGTCTTACCATGCCATCGAGCCGTTGCGTATCATCTTCCTCATGCCGGAGCTT
TCTTCTGGTTGGTGTCTACTGATTCGTCCCTGTTGGTCATGGCAAGAGTCATTATTG
ACAACAAAGATGGACCAACACAGAAATATCTGCTGATCTTGGAGCGTTGTCTGTCTATA
TCCAAGAAATGTTCCGATTCGATATTATAAACTCTAAAAAAAGCCAGTGAAGGTTGAAGA
GTATAAACCCAGGTGAGACAGCACCCCTATGCGACTGCTGGCTATGTTCTGGCTGGGCT
TTGGAATCATGAGTGGAGTATTTCTTGTGAATACCCCTATCTGACTCCTGGGCCAGGCA
CAGTGGGCATTCATGGAGATTCTCCTCAATTCTCCTTATTCACTGCTTCATGACGCTGGTCA
TTATCTTGCTGCATGTATTCTGGGCATTGTATTTTGATGGCTGTGAGAAGAAAAAGTGGG
GCATCCTCCTTATCGTTCTCCTGACCCACCTGCTGGTGTCAAGCCCAGACCTTCATAAGTTCTT
ATTATGGAATAAACCTGGCGTCAGCATTATAATCCTGGTGTCACTGGCACCTGGCATTCT
TAGCTGCGGGAGGCAGCTGCCGAAGCCTGAAACTCTGCCTGCTGCAAGACAAGAACCTTC
TTCTTACAACCAGCGCTCCAGATAACTCAGGGAACCAGCAGTCCAAACCGCAGACTACA
TCTTAGAGGAAGCACAACTGTGCCTTTCTGAAAATCCCTTTCTGGTGGATTGAGAAA
GAAATAAAACTATGCAGATA

-

FIGURE 94

MTAAVFFGCAFIAFGPALALYVFTIAIEPLRIIFLIAGAFFWLVSLLISSLVWFMARVIIDNK
DGPTQKYLIFGAFVSVYIQEMFRFAYYKLLKKASEGLKSINPGETAPSMRLLAYVSGLGFGI
MSGVFSFVNTLSDSLGP GTVGIHGDSPQFFLYSAFMTLVIIILLHVFWGIVFFDGCEKKKGIL
LIVLLTHLLVSAQTFIISYYGINLASAFIILVLMGTWAFLAAGGSCRSLKLCLLCQDKNFLY
NQRSR

Important features of the protein:

Signal peptide:

amino acids 1-19

Transmembrane domains:

amino acids 32-51, 119-138, 152-169, 216-235

Glycosaminoglycan attachment site.

amino acids 120-123

Sodium:neurotransmitter symporter family protein

amino acids 31-65

FIGURE 95

AATTTTCACCAGAGTAAACTTGAGAAACCAACTGGACCTTGAGTATTGTACATTTGCCTCG
TGGACCCAAAGGTAGCAATCTGAAACATGGAGGAGTACGATTCTACTGTTTGTCTTAGGAT
CAAACTCGGTCATTACCACAGCTCAAACCTGCTTGGACTCCCTCCCACAAAATGGCTCCGG
ATCAGGGAACACTACCAAACCAACAGCAGTCAAATCAGGTCTTCCTTAAAGTCTGATAC
CATTAACACAGATGCTCACACTGGGCCAGATCTGCATCTGTTAAATCCTGCTGCAGGAATGA
CACCTGGTACCCAGACCCACCCATTGACCTGGAGGGTTGAATGTACAACAGCAACTGCACC
CACATGTGTTACCAATTTGTCACACAACTTGGAGCCCAGGGCACTATCCTAAGCTCAGAGG
AATTGCCACAAATCTCACGAGCCTCATCATCCATTCCATTGTTCCGGAGGCATCCTGCCA
CCAGTCAGGCAGGGCTAATCCAGATGTCCAGGATGGAAGCCTCCAGCAGGAGGAGCAGGTG
TAAATCCTGCCACCCAGGGAACCCCAGCAGGCCGCCTCCAACTCCCAGTGGCACAGATGACG
ACTTTGCAGTGACCACCCCTGCAGGCATCCAAAGGAGCACACATGCCATCGAGGAAGGCCACCA
CAGAATCAGCAAATGGAATTCAGTAAGCTGTTCAAATTTCAACTAAGCTGCCTCGAATT
TGGTGATACATGTGAATCTTATCATTGATTATATTGGAATAGATTGAGACACATTGGATA
GTCTTAGAAGAAATTAAATTCTTAATTACCTGAAAATATTCTTGAAATTCAAGAAAATATGTT
CTATGTAGAGAATCCAACCTTTAAAAACAATAATTCAATGGATAATCTGTCTTGAAATAT
AACATTATGCTGCCTGGATGATATGCATATTAAAACATATTGGAAAATGGAAAAAAA
AAA

96/168

FIGURE 96

MRSTILLFCLLGSTRSLPQLKPALGLPPTKIALPDQGTLPNQQQSNQVFPSLSLIPLTQM
LTLGPDLHLLNPAAGMTPGTQTHPLTLGGLNVQQQLHPHVLPIFVTQLGAQGTILSSEE
LPQIIFTSLIIHSLFPGGILPTSQAGANPDVQDGSLPAGGAGVNPATQGTPAGRLPTPSG
TDDDFAVTPAGIQRSTHAIIEATTESANGIQ

Signal peptide:

amino acids 1-16

FIGURE 97

GCTCAAGTGCCTGCCTGCCACCCAGCCCAGCCTGGCCAGAGGCCCTGGAGAAGGAGCT
CTCTTCTTGCCTGGCAGCTGGACCAAGGGAGCCAGTCTTGGCGCTGGAGGGCTGTCCTGAC
CATGGTCCCTGCCTGGCTGTGGCTGCTTGTCTCCGTCCCCAGGCTCTCCCAAGGCCA
GCCCTGCAGAGCTGTCTGTGGAAAGTTCCAGAAAATGTTGGAAATTCCCTTATACCTGAC
CAAGTTGCCGCTGCCCGTGAGGGGGCTGAAGGCCAGATCGTGTGTCAGGGACTCAGGCCA
GGCAACTGAGGGCCATTGCTATGGATCCAGATTCTGGCTTCTGCTGGTGACCAGGGCCT
GGACCGAGAGGAGCAGGCAGAGTACCGACTACAGGTACCCCTGGAGATGCAGGATGGACATGT
CTTGTGGGTCCACAGCCTGTGCTGTGACAGTGAAGGATGAGAATGACCAGGTGCCCTATT
CTCTCAAGCCATCTACAGAGCTGGCTGAGCCGGTACCGCCCTGGCATCCCCCTCCTCTT
CCTTGAGGCTTCAGACCGGGATGAGCCAGGCACAGCCAACCTGGATCTTGATTCACATCCT
GAGCCAGGCTCCAGCCCAGCCTCCCCAGACATGTTCCAGCTGGAGCCTCGGCTGGGGCTCT
GCCCTCAGCCCCAAGGGGAGCACCAGCCTGACCACGCCCTGGAGAGGACCTACCAGCTGTT
GGTACAGGTCAAGGACATGGGTGACCAGGCCTCAGGCCACCAGGCCACTGCCACCGTGGAAAGT
CTCCATCATAGAGAGCACCTGGGTGTCCTAGAGCCTATCCACCTGGCAGAGAATCTCAAAGT
CCTATACCGCACCACATGGCCAGGTACACTGGAGTGGGGTGTGCACTATCACCTGGA
GAGCCATCCCCGGGACCTTGAAGTGAATGAGGAAACCTTACGTGACCAGAGAGCT
GGACAGAGAAGGCCAGGCTGAGTACCTGCTCCAGGTGCGGGCTCAGAATTCCATGGCAGAGGA
CTATGCGGCCCTCTGGAGCTGCACGTGCTGGTATGGATGAGAATGACAACGTGCCTATCTG
CCCTCCCCGTGACCCCACAGTCAGCATCCCTGAGCTCAGTCCACCAAGGTACTGAAGTGACTAG
ACTGTCAGCAGAGGATGCAGATGCCCGGCTCCCCAATTCCACGTTGTATCAGCTCCT
GAGCCCTGAGCCTGAGGATGGGTAGAGGGAGAGCCTCCAGGTGGACCCACTCAGGCAG
TGTGACGCTGGGGTGTCCCACCTCGAGCAGGCCAGAACATCCTGCTCTGGTGTGGCCAT
GGACCTGGCAGGCGCAGAGGTGGCTTCAGCAGCACGTGTGAAGTCAAGTCGAGTCACAGA
TATCAATGATCACGCCCTGAGTTCATCACTTCCAGATTGGCCTATAAGCCTCCGTGAGGA
TGTGGAGCCCAGGACTCTGGTGGCATGCTAACAGCATTGATGCTGACCTCGAGCCCGCCTT
CCGCCTCATGGATTTCGCATTGAGAGGGAGACACAGAACGGACTTTGGCCTGGATTGGGA
GCCAGACTCTGGCATGTTAGACTCAGACTCTGCAAGAACCTCAGTTATGAGGCAGCTCCAAG
TCATGAGGTGGTGGTGGCAGAGTGTGGCGAAGCTGGTGGGGCCAGGCCAGGCCCTGG
AGCCACCGCCACGGTGAETGTGCTAGTGGAGAGAGTGTGCCACCCCCAAGTTGGACCAAGGA
GAGCTACGAGGCCAGTGTCCCCATCAGTGCCTCAGGCCCTTCTGCTGACCACATCCAGCC
CTCCGACCCCATCAGCGAACCTCAGGTTCTCCCTAGTCATGACTCAGAGGGCTGGCTCTG
CATTGAGAAATTCTCCGGGAGGTGCACACGCCAGTCCCTGCAGGGCGCCAGCCTGGGG
CACCTACACGGTCTGTGGAGGCCAGGATACAGCCCTGACTCTTGCCTGGGGCTGGCCCTCCA
ATACCTCTGCACACCCCCCAAGACCATGGCTTGTGAGTGGACCCAGCAAGGACCCCA
TCTGGCCAGTGGCACGGTCCCTACAGCTTACCCCTGGTCCCACCCCCACGGTGCACAGGG
TTGGCGCTCCAGACTCTCAATGGTCCCAGTGCCTACCTCACCTGGCCCTGCATTGGGTGGA
GCCACGTGAACACATAATCCCCGTGGTGGTCAAGGCCACAATGCCAGATGTGGCAGCTCTGGT
TCGAGTGATCGTGTGCGCTGCAACGTGGAGGGCAGTGCATGCGCAAGGTGGCCGATGAA
GGGCATGCCACGAAGCTGCGCAGTGGCATCCTGTAGGCACCCCTGGTAGCAATAGGAAT
CTTCCATCCTCATTTCACCCACTGGACCATGTCAGGAAAGAAGGACCCGGATCAACCAGC
AGACAGCGTGCCCTGAAGGCAGTGTCTAGCT**TGA**ATGGCCCAGGCAGCTCTAGCTGGGAGCTTGGC
CTCTGGCTCCATCTGAGTCCCCCTGGAGAGAGGCCAGCAGCACCAAGATCCAGCAGGGACAGGA
CAGAGTAGAAGCCCCCTCCATCTGCCCTGGGTGGAGGCACCATCACCACACCAGGCATGTCT
GCAGAGCCTGGACACCAACTTTATGGACTGCCCATGGAGTGCTCCAAATGTCAGGGTGTGTTG
CCCAATAATAAGCCCCAGAGAACTGGCTGGCCCTATGGGAAAAA
AAAAAAAAAAAAAG

98/168

FIGURE 98

MVPAWLWLLCVSVPQALPKAQPAELSVEVPENYGGNFPPLYLTKLPLPREGAEGQIVLSGDSGK
ATEGPFAMDPSGFLVTRALDREEQAEYQLQVTLEMQDGHVLWGPQPVLVHKDENDQVPHF
SQAIYRARLSRGTRPGIPFLFLEASDRDEPGTANSDLRFHILSQAPAQPSPDMFQLEPRLGAL
ALSPKGSTSLDHALERTYQLLVQVKDMGDQASGHQATATVESSIESTWVSLEPIHLAENLKV
LYPHHMAQVHWSGGDVHYHLESHPPGPFEVNAEGNLYVTRELDREAQAEYLLQVRAQNSHGED
YAAPPLEHVLVMDENDNVPICPPRDPVTISIPELSPPGTEVTRLSAEDADAPGSPNSHVYQOLL
SPEPEDGVEGRAFQVDPTSGSVTLGVPLRAGQNILLVLAMDLAGAEGGFSSCTCEVEAVTD
INDHAPEFITSQIGPISLPEDVEPGTLVAMLTAIDADLEPAFRLMDFAIERGDTEGTFGLDWE
PDSGHVRLRLCKNLSYEAPSHEVVVVVQSVAKLVGPGPGPAGATATVTVLVERVMPPPQLDQE
SYEASVPISAPAGSFLLTIQPSDPISRTLRFSLVNDSEGWLICIEKFSGEVHTAQSLQGAQPGD
TYTVLVEAQDTALTLPVPSQYLCTPRQDHGLIVSGPSKDPDLASGHGPYSFTLGPNPTVQRD
WRLQTLNGSHAYLTIALHWVEPREHIIIPVVVSHNAQMWMQLLVRVIVCRCNVEGQCMRKVGRMK
GMPTKLSAVGILVGTLVAIGIFLILIFTHWMSRKKDQPADSVPLKATV

Signal peptide:

amino acids 1-18

Transmembrane domain:

amino acids 762-784

FIGURE 99

GGCTGACCGTGCTACATTGCCTGGAGGAAGCCTAAGGAACCCAGGCATCCAGCTGCCACGCC
TGAGTCCAAGATTCTTCCCAGGAACACAAACAGTAGGAGACCCACGCTCTGGAAAGCACCAGCC
TTTATCTCTCACCTTCAAGTCCCCTTCTAAGAATCCTCTGTTCTTGCCTCTAAAGTCT
TGGTACATCTAGGACCCAGGCATCTGCTTCCAGCACAAGAGACAG **TGA**AGATGCAGAA
AGGAAATGTTCTCCTATGTTGGTCTACTATTGCATTAGAAGCTGCAACAAATTCCAATGA
GACTAGCACCTCTGCCAACACTGGATCCAGTGTGATCTCCAGTGGAGCCAGCACGCCACCAA
CTCTGGGTCCAGTGTGACCTCCAGTGGGGTCAGCACAGCCACCATCTCAGGGTCCAGCGTGAC
CTCCAATGGGGTCAGCATAGTCACCAACTCTGAGTCCATACAACCTCCAGTGGGATCAGCAC
AGCCACCAACTCTGAGTTCAGCACAGCGTCCAGTGGGATCAGCATAGCCACCAACTCTGAGTC
CAGCACACCTCCAGTGGGCCAGCACAGCCACCAACTCTGAGTCCAGCACACCCCTCCAGTGG
GGCCAGCACAGTCACCAACTCTGGGTCCAGTGTGACCTCCAGTGGAGCCAGCAGTGCACCAA
CTCTGAGTCCAGCACAGTGTCCAGTAGGGCCAGCAGTGCACCAACTCTGAGTCTAGCACACT
CTCCAGTGGGCCAGCACAGCCACCAACTCTGACTCCAGCACAAACCTCCAGTGGGCTAGCAC
AGCCACCAACTCTGAGTCCAGCACAAACCTCCAGTGGGCCAGCACAGCCACCAACTCTGAGTC
CAGCACAGTGTCCAGTAGGGCCAGCAGTGCACCAACTCTGAGTCCAGCACACCCCTCCAGTGG
GGCCAGCACAGCCACCAACTCTGAGTCCAGAACGACCTCCAAATGGGGTGGCACAGCCACCAA
CTCTGAGTCCAGCACGACCTCCAGTGGGCCAGCACAGCCACCAACTCTGACTCCAGCACAGT
GTCCAGTGGGCCAGCAGTGCACCAACTCTGAGTCCAGCACACCCCTCCAGTGGGCCAGCAC
AGCCACCAACTCTGAGTCCAGCACGACCTCCAGTGGGCTAGCACAGCCACCAACTCTGACTC
CAGCACACCTCCAGTGGGCCAGCACAGCCACCAACTCTGAGTCCAGCACAGTGTCCAGTGG
GATCAGCACAGTCACCAATTCTGAGTCCAGCACACCCCTCCAGTGGGCCAACACAGCCACCAA
CTCTGAGTCCAGTACGACCTCCAGTGGGCCAACACAGCCACCAACTCTGAGTCCAGCACAGT
GTCCAGTGGGCCAGCAGTGCACCAACTCTGAGTCCAGCACACCCCTCCAGTGGGTAGCAC
AGCCACCAACTCTGAGTCCAGCACACCCCTCCAGTGGGCCAGCACAGCCACCAACTCTGACTC
CAGCACACCTCCAGTGGGCCAGCACAGCCACCAACTCTGAGTCCAGCACAGTGTCCAGTGG
GATCAGCACAGTCACCAATTCTGAGTCCAGCACACCCCTCCAGTGGGCCAACACAGCCACCAA
CTCTGGGTCCAGTGTGACCTCTGCAGGCTCTGGAACAGCAGCTCTGACTGGAATGCACACAAC
TTCCCATAGTCATCTACTGCAGTGAGTGAGGCAAAGCCTGGTGGTCCCTGGGCCGTGGGA
AATCTTCCTCATCACCCCTGGTCTCGGTTGTGGCGGCCGTGGGCTTTGCTGGCTTTCT
CTGTGTGAGAAACAGCCTGTCCCTGAGAAACACCTTTAACACAGCTGTCTACCACCCCTCATGG
CCTCAACCATGGCCTTGGTCCAGGCCCTGGAGGGAAATCATGGAGCCCCCACAGGCCAGGTG
GAGTCCTAACTGGTTCTGGAGGGAGACCAGTATCATCGATAGCCATGGAGATGAGCAGGAGGAA
CAGCGGGCCCT**TGA**AGCAGCCCCGGAAAGCAAGTGCCGATTCTCAGGAAGGAAGAGACCTGGGC
ACCCAAGACCTGGTTCTTCATTCATCCCAGGAGACCCCTCCAGCTTGTGAGATCCT
GAAAATCTTGAAGAAGGTATTCTCACCTTCTTGCCTTACAGACACTGGAAAGAGAATAC
TATATTGCTCATTAGCTAAGAAATAATACATCTCATCTAACACACAGACAAAGAGAAGCT
GTGCTTGCCCCGGGGTGGGTATCTAGCTGTGAGATGAACTCAGTTATAGGAGAAAACCTCCAT
GCTGGACTCCATCTGGCATTCAAATCTCCACAGTAAAATCAAAGACCTCAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAA

100/168

FIGURE 100

MKMQGNVLLMFGLLHLEAATNSNETSTSANTGSSVISSGASTATNSGSSVTSSGVSTATIS
GSSVTSNGVSIVTNSEFHTTSSGISTATNSEFSTASSGISIATNSESSTTSSGASTATNSESS
TPSSGASTVTNSGSSVTSSGASTATNSESSTVSSRASTATNSESSTLSSGASTATNSDSSTS
SGASTATNSESSTTSSGASTATNSESSTVSSRASTATNSESSTTSSGASTATNSESRTTSNGA
GTATNSESSTTSSGASTATNSDSSTVSSGASTATNSESSTTSSGASTATNSESSTTSSGASTA
TNSDSSTTSSGAGTATNSESSTVSSGISTVTNSESSTPSSGANTATNSESSTTSSGANTATNS
ESSTVSSGASTATNSESSTTSSGVSTATNSESSTTSSGASTATNDSSTSSEASTATNSESS
TVSSGISTVTNSESSTTSSGANTATNSGSSVTSAGSGTAALTGMHTTSHSASTAVSEAKPGGS
LVPWEIFLITLVSVVAAVGLFAGLFFCVRNSLSLRNTFNTAVYHPHGLNHGLGPGPGGNHGAP
HRPRWSPNWFWRPVPSSIAMEMSGRNSGP

Signal peptide:

amino acids 1-20

Transmembrane domain:

amino acids 510-532

FIGURE 101

GGCCGGACGCCCTCCGCGTTACGGGATGAATTAACGGCGGGTTCCGCACGGAGGTTGTGACCCCC
TACGGAGCCCCAGCTGCCACGCACCCACTCGCGTCGCGCGCGTGCCTGCTGTACAC
GGTGGGAGGCTGGAACATATCAGGCTGAAAAACAGAGTGGGTACTCTCTGGGAAGCTGGCA
ACAAATGGATGATGTGATATATGCATTCCAGGGAAAGGGAAATTGTGGTCTGAACCCAT
GGTCAATTAACGAGGCAGTTCTAGCTACTGCACGTACTCATAAAGCAGGACTCTAAAGCT
TTGGAATCATGGTGTATGGAAAGGGATTACTTATACTGACTCTGTTGGGAAGCTTT
TTGGAAGCATTTCATGCTGAGTCCCTTTACCTTGATGTTGTAAACCCATCTGGTATC
GCTGGATCAACAACCGCCTGTGGCAACATGGCTCACCTACCTGTGGCATTATTGGAGACCA
TGTTGGTGTAAAAGTGATTATAACTGGGATGCATTGTTCTGGAGAAAGAAGTGTCTTA
TCATGAACCACCGGACAAGAATGGACTGGATGTTCTGTGGAATTGCCTGATGCGATATAGCT
ACCTCAGATTGGAGAAAATTGCCTCAAAGCGAGTCTCAAAGGTGTTCTGGATTGGTTGGG
CCATGCAGGCTGCTGCCTATATCTCATTAGGAAATGGAAGGATGACAAGAGCCATTG
AAGACATGATTGATTACTTTGTGATATTCACTGGAACTTCAACTCCTCATATCCCAGAAG
GGACTGATCTCACAGAAAACAGCAAGTCTCGAAGTAATGCATTGCTGAAAAAAATGGACTTC
AGAAAATGAATATGTTTACATCCAAGAACTACAGGCTTACTTTGTGGTAGACCGTCTAA
GAGAAGGTAAGAACCTTGATGCTGTCCATGATATCACTGTGGCGTACCTCACAAACATTCTC
AATCAGAGAACGACCTCCTCCAAGGAGACTTCCCAGGGAAATCCACTTCACGTCCACCGGT
ATCCAATAGACACCCCTCCCCACATCCAAGGAGGACCTCAACTCTGGTGCACAAACGGTGGG
AAGAGAAAAGAGAGAGGCTCGTTCCTCTATCAAGGGAGAAGAATTTTATTACCGGAC
AGAGTGTCTTCCACCTTGCAAGTCTGAACTCAGGGCTTGTGGTCAAATTGCTCTATAC
TGTATTGGACCCCTGTTCAAGCCTGCAATGTGCCTACTCATATATTGTACAGTCTGTAAAGT
GGTATTGATTCACCATTGTAATCTTGTGCTGCAAGAGAGAATATTGGTGGACTGGAGA
TCATAGAACCTGCATGTTACCGACTTTACACAAACAGCCACATTAAATTCAAAGAAAATG
AGTAAGATTATAAGGTTGCCATGTGAAAACCTAGAGCATATTGGAAATGTTCTAACCTT
TCTAAGCTCAGATGCATTTGCATGACTATGTCGAATATTCTTACTGCCATCATTATTGT
TAAAGATATTGCACTTAATTGTGGAAAAATATTGCTACAATTTTAAATCTCTGAA
TGTAATTCGATACTGTGTACATAGCAGGGAGTGATGGGGTGAATAACTGGGCCAGAATA
TTATTAAACAATCATCAGGCTTTAAA

102/168

FIGURE 102

MHSRGREIVVLLNPWSINEAVSSYCTYFIKQDSKSFGIMVSWKGIYFILTLFWGSFFGSIFML
SPFLPLMFVNPSWYRWINNRLVATWLTPVALLETMFGVKVIITGDAFVPGERSVIIMNHRTR
MDWMFLWNCLMRYSYLRLEKICLKASLKGVPFGWAMQAAAYIFIHRWKDDKSHFEDMIDYF
CDIHEPLQLLIFPEGTDLTENSRSNAFAEKNGLQKYEYVLHPRTTGFTVVVDRLREGKNLD
AVHDITVAYPHNIHQSEKHLIQLQDFPREIHFHVRYPIDTLPTSKEDEIQLWCHKRWEEKERL
RSFYQGEKNFYFTGQSVIPPKSELRLVVKLLSILYWTLFSPAMCLLIYLYSLVKWYFIITI
VIFVLQERIFGGLEIIELACYRLLHKQPHLNSKKNE

Important features of the protein:

Signal peptide:

amino acids 1-22

Transmembrane domains:

amino acids 44-63, 90-108, 354-377

FIGURE 103

CGGCTCGAGCGGCTCGAGTGAAGAGCCCTCCACGGCTCTGCGCTGAGACAGCTGGCCTGA
CCTCCAAATCATCCATCCACCCCTGCTGTCACTGTTTCAAGTGTGAGATCAACCCACAGG
AATATCC**ATGG**CTTTGTGCTCATTGGTTCTCAGTTCTACGAGCTGGTGTCAAGACAGTG
GCAAGTCACTGGACCGGGCAAGTTGTCCAGGCCTGGTGGGGAGGACGCCGTGTTCTCCTG
CTCCCTCTTCCTGAGACCAGTGCAGAGGCTATGGAAGTGCGGTTCTCAGGAATCAGTCCA
TGCTGTGGTCCACCTCTACAGAGATGGGAAGACTGGGAATCTAAGCAGATGCCACAGTATCG
AGGGAGAACTGAGTTGTGAAGGACTCCATTGCAGGGGGCGTGTCTCTAAGGCTAAAAAA
CATCACTCCCTCGGACATCGGCCTGTATGGGTGCTGGTCAGTCCCAGATTACGATGAGGA
GGCCACCTGGAGCTGCGGGTGGCAGCACTGGCTCACTCCTCTCATTCCATCGTGGATA
TGTTGACGGAGGTATCCAGTTACTCTGCCTGCTCAGGCTGGTCCCCAGCCCACAGCAA
GTGGAAAGTCCACAAGGACAGGATTGTCTCAGACTCCAGAGCAAATGCAGATGGTACAG
CCTGTATGATGTGGAGATCTCATTATAGTCCAGGAAAATGCTGGAGCATATTGTGTTCCAT
CCACCTTGCAGCAGAGTCATGAGGTGGAATCCAAGGTATTGATAGGAGAGACGTTTCCA
GCCCTCACCTGGCGCTGGCTTCTATTTACTCGGGTTACTCTGTGGTGCCTGTGGTGT
TGTCACTGGGATGATAATTGTTTCTCAAATCCAAGGAAAATCCAGGCGGAACCGCAGTGGAGGTGACTCT
GAGAAGAAAGCACGGACAGGCAGAATTGAGAGACGCCGGAAACACGCAGTGGAGGTGACTCT
GGATCCAGAGACGGCTACCCGAAGCTCTGCCTTGATCTGAAAATGTAACCCATAGAAA
AGCTCCCCAGGAGGTGCCTACTCTGAGAAGAGATTACAAGGAAGAGTGTGGGGCTCTCA
GGGTTCCAAGCAGGGAGACATTACTGGAGGTGGACGTGGACAAAATGTAGGGTGGTATGT
GGGAGTGTGTCGGGATGACGTAGACAGGGGAAGAACAAATGTGACTTGTCTCCAACAATGG
GTATTGGGTCTCAGACTGACAACAGAACATTGTATTCACATTCAATCCCCATTATCAG
CCTCCCCCCCAGCACCCCTCTACACGAGTAGGGTCTCCTGGACTATGAGGGTGGACCAT
CTCCTTCTCAATACAAATGACCAGTCCCTTATTATACCCCTGCTGACATGTCAGTTGAAGG
CTTGTGAGACCCTATATCCAGCATGCGATGTATGACGAGGAAAAGGGGACTCCATATTCA
ATGTCCAGTGTCTGGGAT**TGA**GACAGAGAACCCCTGCTTAAAGGGCCCACACCACAGACC
CAGACACAGCCAAGGGAGAGTGCCTCCGACAGGTGGCCCCAGCTCCTCCGGAGCCTGCGC
ACAGAGAGTCACGCCCAACTCTCCTTAGGGAGCTGAGGTTCTCTGCCCTGAGCCCTGCA
GCAGCGGAGTCACAGCTCAGATGAGGGGGATTGGCCTGACCTGTGGAGTCAGAACCC
ATGGCTGCCCTGAAGTGGGAGGAATAGACTCACATTAGGTTAGTTGTGAAAATCCATC
CAGCTAACGATCTGAACAAAGTCACAACCTCCAGGCTCTCATTGCTAGTCACGGACAGT
GATTCTGCCCTCACAGGTGAAGATTAAAGAGACAAAGCAATGTGAATCATGCTTGAGGTTGA
GGGCACAGTGTGCTAATGATGTGTTTATATTACATTTCACCATAAAACTCTGTT
GCTTATTCCACATTAATTACTTTCTATACCAAAATCACCACGGAAATAGTTATTGAACAC
CTGCTTGTGAGGCTAAAGAATAAAGAGGGAGGTAGGATTTCACTGATTCTATAAGCCAG
CATTACCTGATAACAAAACCAGGCAAAGAAAACAGAAGAAGAGGAAGGAAAACACAGGTCCA
TATCCCTCATTAACACAGACACAAAATTCTAAATAAAATTAAACAAATTAAACTAAACAAAT
ATATTAAAGATGATATATAACTACTCAGTGTGGTTGTCCCACAAATGCAGAGTTGGTTAA
TATTAAATATCAACCAGTGTAAATTCAAGCACAATTAAAGTAAAAAGAAAACCATAAAAAAA
AAAAAA

104/168

FIGURE 104

MAFVLILVLSFYELVSGQWQVTGPGKFVQALVGEDAVFSCSLFPETSAEAMEVRFFRNQFHAV
VHLYRDGEDWESKQMPQYRGRTEFKDSIAGGRVSLRLKNITPSDIGLYGCWFSSQIYDEEAT
WELRVAALGSLPLISIVGYVDGGIQLLCLSSGWFPQOPTAKWKGPQGQDLSSDSRANADGYSLY
DVEISIIVQENAGSILCSIHLAEQSHEVESKVLIGETFFQPSPWRLASILLGLLCALCGVVM
GMIIVFFKSKGKIQAELDWRRKHGQAEELRDARKHAVEVTLDPETAHPKLCVSDLKTVTHRKAP
QEVPHSEKRFTRKSVVASQGFQAGRHYWEVDVGQNVGWYVGCRDDVDRGKNNVTLSNNGYW
VRLLTTEHLYFTFNPHFISLPPSTPPTRGVFLDYEGGTISFFNTNDQSLIYTLLTCQFEGLL
RPYIQHAMYDEEKGTPIFICPVSWG

Signal peptide:

amino acids 1-17

Transmembrane domains:

amino acids 131-150, 235-259

FIGURE 105

CCTTCACAGGACTCTCATTGCTGGTGGCAATGATGTATCGGCCAGATGTGGTGAGGGCTAG
GAAAAGAGTTGGGGACCCCTGGGTTATCGGCCTCGTCATCTCATATCCCTGATTGTCCT
GGCAGTGTGCATTGGACTCACTGTTCATTATGTGAGATATAATCAAAAGAAGACCTACAATTA
CTATAGCACATTGTCATTACAAC TGACAAACTATATGCTGAGTTGGCAGAGAGGGCTCTAA
CAATTTACAGAAATGAGCCAGAGACTTGAATCAATGGTAAAAATGCATTTATAAATCTCC
ATTAAGGGAGAATTGTCAAGTCTCAGGTTATCAAGTTCAAGCAGAAGCATGGAGTGT
GGCTCATATGCTGTTGATTGTAGATTTCACTCTACTGAGGATCCTGAAACTGTAGATAAAAT
TGTCAACTTGTACATGAAAAGCTGCAAGATGCTGTAGGACCCCCCTAAAGTAGATCCTCA
CTCAGTTAAAATAAAAAAATCAACAAGACAGAAACAGACAGCTATCTAAACCATTGCTGCGG
AACACGAAGAAGTAAAACCTAGGTCAAGACTCAGGATCGTTGGGGACAGAAGTAGAAGA
GGGTGAATGCCCTGGCAGGCTAGCCTGCAGTGGGATGGAGTCATCGCTGTGGAGAACCTT
AATTAATGCCACATGGCTTGAGTGCTGCTCACTGTTACAACATATAAGAACCTGCCAG
ATGGACTGCTTCCTTGGAGTAACAATAAACCTTCGAAAATGAAACGGGTCTCCGGAGAAT
AATTGTCCATGAAAATACAAACACCCATCACATGACTATGATATTCTCTTGAGAGCTTC
TAGCCCTGTTCCCTACACAAATGCAGTACATAGAGTTGTCTCCCTGATGCATCCTATGAGTT
TCAACCAGGTGATGTGATGTTGTGACAGGATTGGAGCACTGAAAATGATGGTTACAGTCA
AAATCATCTCGACAAGCACAGGTGACTCTCATAGACGCTACAACTTGCAATGAACCTCAAGC
TTACAATGACGCCATACTCCTAGAATGTTATGTGCTGGCTCCTAGAAGGAAAACAGATGC
ATGCCAGGGTGAECTGGAGGACACTGGTTAGTTCAAGATGCTAGAGATATCTGGTACCTG
TGGAAATAGTGAGCTGGGGAGATGAATGTGCGAAACCCAAACAAGCCTGGTGTACTAGAGT
TACGGCCTTGCAGGACTGGATTACTCAAAAATGGTATCTAAGAGACAAAAGCCTCATGGAA
CAGATAACATTTTTGGTTGGGTGTGGAGGCCATTTAGAGATACAGAATTGGAGA
AGACTTGCAAAACAGCTAGATTGACTGATCTCAATAAAACTGTTGCTGATGCATGTATTT
CTTCCCAGCTCTGTCACGTAAGCATCCTGCTGCCAGATCAACTCTGTCATCTGTGA
GCAATAGTTGAAACTTATGTACATAGAGAAATAGATAATACAATATTACATTACAGCCTGTA
TTCATTGTTCTAGAAGTTGTGAGAATTGACTGTTGACATAAATTGTAATGCATA
TATACAATTGAAGCACTCCTTTCTCAGTCCTCAGCTCCTCTCATTCAGCAAATATCCA
TTTCAGGTGCAAGAACAGGAGTGAAAGAAAATATAAGAAGAAAAATCCCCTACATTTA
TTGGCACAGAAAAGTATTAGGTGTTCTTAGTGGAAATATTAGAAATGATCATATTCA
GAAAGGTCAAGCAAAGACAGCAGAATACCAATCACTCATCATTAGGAAGTATGGGAAC
GTTAAGGAAGTCCAGAAAGAAGCCAAGATATATCCTTATTTCAACAAACAAC
ATAAAATGTGAAGAAGATTCTGTTTTGTGACCTATAATTACAAACTTCATGCAATG
TACTGTTCTAAGCAAATTAAAGCAAATTAAACATTGTTACTGAGGATGTCAACATA
TAACAAATAAAATATAATCACCCA

106/168

FIGURE 106

MMYRPDVVRARKRVCWEPWVIGLVIFISLIVLAVCIGLTVHYVRYNQKKTYNYYSTLSFTTDK
LYAEFGREASNNFTEMSRQLESMVKNAYKSPLEEKFVKSQVIKFSSQQKHGVLAHMLLICRFH
STEDPETVDKIVQLVLHEKLQDAVGPPKVDPHSVKIKKINKTETDSYLNHCCGTRRSKTLGQS
LRIVGGTEVEEGEWPWQASLQWDGSHRCGATLINATWLVSAAHCFTTYKNPARWTASFGVTIK
PSKMKRGLRRIIVHEKYKHPHDYDISLAELSSPVYTNAVHRVCLPDASYEFQPGDVMFVTG
FGALKNDGYSQNHLRQAQVTLIDATTNEPQAYNDAITPRMLCAGSLEGKTDACQGDSGGPLV
SSDARDIWLALGIVSWGDECAKPNKPGVYTRVTALRDWITSKTGI

Transmembrane domain:

amino acids 21-40 (type II)

FIGURE 107

AGAGAAAGAAGCGTCTCCAGCTGAAGCCAATGCAGCCCTCCGGCTCTCCCGAAGAAGTCCCC
TGCCCCGATGAGCCCCCGCCGTGCGTCCCCGACTATCCCCAGGCAGGGCGTGGGGCACCGGGCC
CAGGCCGACGATCGCTGCCGTTTGCCTGGGAGTAGGATGTGGTAAAGGAATGGGCTTC
TCCCTTACGGGCTCACAAATGGCCAGAGAAGATTCCGTGAAGTGTCTGCGCTGCCTGCTCTAC
GCCCTCAATCTGCTCTTGGTTAATGTCCATCAGTGTGGCAGTTCTGCTTGGATGAGG
GACTACCTAAATAATGTTCTCACTTTAAGCAGAACGAGGGTAGAGGAAGCAGTCATTG
ACTTACTTTCTGTGGTCATCCGGTCATGATTGCTGTTGCTGTTCCATTATGTTGGGG
ATGTTAGGATATTGTGGAACGGTAAAAGAAATCTGTTGCTTGCATGGTACTTTGGAAGT
TTGCTTGTCAATTCTGTGTTAGAACTGGCTTGTGGCAGATATGAACAGGAACATTATG
GTTCCAGTACAATGGTCAGATATGGTCACTTTGAAAGCCAGGATGACAAATTATGGATTACCT
AGATATCGGTGGCTTACTCATGCTTGAATTTCAGAGAGAGTTAAGTGCTGTGGAGTA
GTATATTCACTGACTGGTTGAAATGACAGAGATGGACTGGCCCCAGATTCCGTGTGTT
AGAGAATTCCCAGGATGTTCAAACAGGCCACCAGGAAGATCTCAGTGACCTTATCAAGAG
GGTTGTGGGAAGAAAATGTATTCCTTTGAGAGGAACCAAACACTGCAGGTGCTGAGGTTT
CTGGGAATCTCCATTGGGTGACACAAATCCTGGCATGATTCTCACCATTACTCTGCTCTGG
GCTCTGTATTATGATAGAAGGGAGCCTGGACAGACAAATGATGTCCTGAAGAATGACAAC
TCTCAGCACCTGTCACTGTCAGTAGAACTGTTGAAACCAAGCCTGTCAGAATCTTGAA
CACACATCCATGGCAAACAGCTTAATACACACTTGAGATGGAGGAGTTATAAAAGAAATG
TCACAGAAGAAAACCACAAACTGTTTATTGGACTGTGAATTGGAGTACATACTATGTG
TTTCAGAAATATGTAGAAATAAAATGTTGCCATAAAATAACACCTAACGATATACTATTCTA
TGCTTAAATGAGGATGGAAAAGTTCATGTCATAAGTCACCACCTGGACAATAATTGATGC
CCTTAAATGCTGAAGACAGATGTCACTACCCACTGTGTAGCCTGTATGACTTTACTGAAC
ACAGTTATGTTGAGGCAGCATGGTTGATTAGCATTCGCATCCATGCAAACGAGTCACA
TATGGTGGACTGGAGCCATAGTAAAGGTTGATTTACCTAACACTAGTATAAAAGTACT
AATTAATGCTAACATAGGAAGTTAGAAAATACTAATAACTTTATTACTCAGCGATCTATT
TTCTGATGCTAAATAATTATATCAGAAAATTTCAATATTGGTACTACCTAAATGTGAT
TTTGCTGGTTACTAAATATTCTACCACTAAAGAGCAAGCTAACACATTGCTTAAGCT
GATCAGGGATTTTGATATAAGTCTGTGTTAAATCTGTATAATTCACTGATTCAGTTCT
GATAATGTTAAGAATAACCATTATGAAAAGAAAATTGTCCTGTATAGCATCATTATTTTA
GCCTTCTGTTAATAAGCTTACTATTCTGCTGGCTTATATTACACATATAACTGTTA
TTTAAATCTAACCACTAATTGAAAATTACAGTGTGATACATAGGAATCATTATTCTAGA
ATGAGTCTGGTCTTAGGAAGTATTAATAAGAAAATTGCACATAACTTAGTTGATTGAGAA
AGGACTTGTATGCTGTTCTCCAAATGAAGACTCTTTGACACTAAACACTTTAAAA
AGCTTATCTTGCCTCTCCAAACAAGAAGCAATAGTCTCCAAGTCAATATAAAATTCTACAGA
AAATAGTGTCTTTCTCCAGAAAATGCTGTGAGAATCATTAAACATGTGACAATTAG
AGATTCTTGTGTTATTCACTGATTAATATACTGTGGCAAATTACACAGATTATAAAATT
TTTACAAGAGTATAGTATATTGAAATGGAAAAGTGCATTACTGTATTTGTGTT
TTGTTATTCTCAGAATATGGAAAAGTAAATGTGTCATAAAATATTCTAGAGAG
TAA

108/168

FIGURE 108

MAREDSVKCLRCLLYALNLLFWLMSISVLAWSAWMRDYLNNVLTATRVEEAVILTYFPVV
HPVMIAVCCFLIIVGMLGYCGTVKRNLLLLAWYFGSLLVIFCVELACGVWTYEQELMVPVQWS
DMVTLKARMNTNYGLPRYRWLTHAWNFFQREFKCCGVVYFTDWLEMTEMWDPPDSCCVREFPGC
SKQAHQEDLSLDLYQEGCGKKMYSFLRGTKQLQVLRFILGISIGVTQILAMILTITLLWALYYDR
REPDTDQMMMSLKNDNSQHLSCPSVELLKPSLSRIFEHTSMANSFNTHFEMEEL

Signal peptide:

amino acids 1-33

Transmembrane domains:

amino acids 12-35, 57-86, 94-114, 226-248

FIGURE 109

CCAAGGCCAGAGCTGTGGACACCTTATCCCACTCATCCTCATCCTCTTCTCTGATAAAGGCC
CTACCAAGTGTGATAAAAGTCTTCTCGTGAGAGCCTAGAGGCCCTAAAAAAAGTGTGCTTGA
AAGAGAAGGGGACAAAGGAACACCAGTATTAAGAGGATTTCCAGTGTCTGGCAGTTGGTC
CAGAAGGATGCTCCATTCTGCTTCACCTGCCTCTCATCACAGGCACCTCCGTGTCA
CGTGGCCCTAGATCCTTGTCTGCTTACATCAGCCTGAATGAGCCCTGGAGGAACACTGACCA
CCAGTTGGATGAGTCTCAAGGTCCCTCTATGTGACAACCAGTGAATGGGAGTGGTACCA
CTTCACGGGATGGCGGAGATGCCATGCCTACCTCTGCATACCAGAAAACCAGTGTGAAC
CCACGCACCTGTCTGGCTCAATGGCAGCCACCCCTAGAAGGGGACGGCATTGTGCAACGCCA
GGCTTGTGCCAGCTCAATGGGAACGTGCTGTCTGGAACACCACGGTGGAAAGTCAAGGTTG
CCCTGGAGGCTACTATGTGATCGTGTGACCAAGCCCAGCGTCTGCTTCCACGTCTACTGTGG
TCATTTTATGACATCTGCAGCAGGACTGCCATGGCAGCTGCTCAGATACCAGCAGTGCAC
ATGCGCTCCAGGAACGTGCTAGGCCCTGACAGGCAGACATGCTTGATGAAAATGAATGTGA
GCAAAACAACGGTGGCTGCAAGTGTGAACTCAAAACTCTACCGCTGTGAGTG
TGGGGTTGGCGTGCTAAGAAGTGTGAGGACTGTGAAGACGTTGAAGGATGCCACAA
TAACAATGGTGGCTGCAGCCACTCTGCCTGGATCTGAGAAAGGCTACCAGTGTGAATGTCC
CCGGGGCCTGGTGCTGTCTGAGGATAACCACACTTGCCAAGTCCCTGTGTTGTGCAAATCAA
TGCCATTGAAGTGAACATCCCCAGGGAGCTGGTGGTGGCCTGGAGCTTCTGACCAACAC
CTCCTGCCAGGGAGTGTCCAACGGCACCCATGTCAACATCCTCTCTCAAGACATGTGG
TACAGTGGTCATGTGGTGAATGACAAGATTGTGGCCAGCAACCTCGTACAGGTCTACCAA
GCAGACCCGGGGAGCAGCGGGACTTCATCATCCGAACCAGCAAGCTGTGATCCGGTGAC
CTGCGAGTTCCACGCCTGTACACCATTCTGAAGGATACGTTCCAAACCTTCGAAACTCCCC
ACTGGAAATCATGAGCCGAAATCATGGGATCTCCATTCACTCTGGAGATCTCAAGGACAA
TGAGTTGAAGAGCCTTACCGGGAGCTCTGCCACCCCTCAAGCTCGTACTCCCTACTT
TGGCATTGAGCCGTGGTGACGTGAGCGGCTTGGAAAGCTTGGTGGAGAGCTGCTTTGCCAC
CCCCACCTCCAAGATCGACGAGGTCTGAAATACTACCTCATCCGGATGGCTGTGTTCAGA
TGACTCGGTAAAGCAGTACACATCCGGATCACCTAGCAAAGCACTTCCAGGTCCCTGTCTT
CAAGTTGTGGCAAAGACCACAAGGAAGTGTCTGCACTGCCGGTTCTGTCTGTGGAGT
GTTGGACGAGCGTCCCGCTGTGCCAGGGTGCACCGGAATGCGTCGTGGGCAGGAGG
AGAGGACTCAGCCGGTCTACAGGGCAGACGCTAACAGGCAGGCCATCCGCATCGACTGGG
GGACTAGTTCGTAGCCATACCTCGAGTCCCTGCATTGGACGGCTCTGCTCTTGGAGCTTCTC
CCCCCACCGCCCTCTAAGAACATCTGCCAACAGCTGGTTCAGACTCACACTGTGAGTCAG
ACTCCCAGCACCACACTCTGATTCTGGTCATTCACTGGGACAGGTACAGCACTGCTG
AACAAATGTGGCCTGGTGGGTTCATCTTCTAGGGTTGAAAACAAACTAAACTGTCCACCCAGAA
AGACACTCACCCATTCCCTCATTTCTTCCACACTAAATACCTCGTGTATGGTGCAATC
AGACCACAAATCAGAAGCTGGTATAATATTCAAGTTACAAACCCTAGAAAAATTAAACAG
TTACTGAAATTATGACTTAAATACCAATGACTCCTTAAATATGTAATTAGTTACCTT
GAAATTCAATTCAAATGCAGACTAATTAGGAAATTGGAAGTGTATCAATAAACAGTAT
ATAATT

110/168

FIGURE 110

MPPFLLTCLFITGTSVSPVALDPCSAYISLNNEPWRNTDHQLDESQGPPLCDNHVNGEWYHFT
GMAGDAMPTFCIPEHCGTHAPVWLNGSHPLEGDGIVQRQACASFNGNCCLWNTTVEVKACPG
GYVYVRLTKPSVCFHVYCGFYDICDEDCHGSCSDTSECTCAPGTVLGPDRQTCFDENECEQN
NGGCSEICVNLKNSYRCECGVGRVLRSDGKTCEDVEGCHNNNGCSHSLGSEKGYQCECPRG
LVLSEDNHTCQVPVLCKSNAIEVNIPRELVGGLEFLTNTSCRGVSNGTHVNILFSLKTCGT
VDVVNDKIVASNLVTGLPKQTPGSSGDFIIRTSKLLIPVTCEFPRLYTISEGYVPNLRNSPLE
IMSRNHGIFPFTLEIFKDNEFEPYREALPTLKLRLDSLYFGIEPVVHVGLESILVESCFATPT
SKIDEVLKYYLIRDGCVSDDSVKQYTSRDHLAKHFQVPVFKFVGKDHKEVFLHCRVLVCGVLD
ERSRCAQGCHRRMRRGAGGEDSAGLQGQTLTGGPIRIDWED

Important features of the protein:

Signal peptide:

amino acids 1-16

N-glycosylation sites.

amino acids 89-93, 116-120, 259-263, 291-295, 299-303

Tyrosine kinase phosphorylation sites.

amino acids 411-418, 443-451

N-myristoylation sites.

amino acids 226-232, 233-239, 240-246, 252-258, 296-302, 300-306,
522-528, 531-537

Aspartic acid and asparagine hydroxylation site.

amino acids 197-209

ZZ domain proteins.

amino acids 431-457

Calcium-binding EGF-like proteins.

amino acids 191-212, 232-253

FIGURE 111

GAGAGAGGCAGCAGCTGCTAGCGGACAAGGATGCTGGCGTGAGGGACCAAGGCCTGCCCT
GCACTCGGGCCTCCTCCAGCCAGTGCTGACCAGGGACTTCTGACCTGCTGCCAGCCAGGACC
TGTGTGGGAGGCCCTCCTGCTGCCTGGGTGACAATCTCAGCTCCAGGCTACAGGGAGACC
GGGAGGATCACAGAGCCAGCATGTTACAGGATCCTGACAGTGATCAACCTCTGAACAGCCTCG
ATGTCAAACCCCTGCGCAAACCCGTATCCCCATGGAGACCTTCAGAAAGGTGGGATCCCCA
TCATCATAGCACTACTGAGCCTGGCGAGTATCATCATTGTGGTTGTCCCTCATCAAGGTGATTC
TGGATAAATACTACTCCTCTGCAGCCTCTCCACTTCATCCGAGGAAGCAGCTGTG
ACGGAGAGCTGGACTGTCCCTGGGGAGGACGAGGAGCACTGTGTCAAGAGCTCCCCGAAG
GGCCTGCAGTGGCAGTCCGCCTCTCCAAGGACCGATCCACACTGCAGGTGCTGGACTCGCCA
CAGGGAACTGGTTCTCTGCCTGTTGACAACCTCACAGAAGCTCTCGCTGAGACAGCCTGTA
GGCAGATGGCTACAGCAGAGCTGTGGAGATTGGCCAGACCAGGACTGGATGTTGAA
TCACAGAAAACAGCCAGGAGCTCGCATCGGAACACTCAAGTGGCCCTGTCTCTCAGGCTCCC
TGGTCTCCCTGCACTGTCTTGCCCTGGGAAGAGCCTGAAGACCCCCCGTGTGGTGGGTGGGG
AGGAGGCCTCTGTGGATTCTTGGCTTGGCAGGTCAAGCATCCAGTACGACAAACAGCACGTCT
GTGGAGGGAGCATTGGACCCCCACTGGTCCTCACGGCAGCCCAGTGTTCAGGAAACATA
CCGATGTGTTCAACTGGAGGTGCAGGCTCAGACAAACTGGCAGCTTCCATCCCTGG
CTGTGGCCAAGATCATCATCATTGAATTCAACCCATGTACCCAAAGACAATGACATGCC
TCATGAAGCTGCAGTCCCACACTTTCTCAGGCACAGTCAGGCCATCTGTCTGCCCTTCT
TTGATGAGGAGCTCACTCCAGCCACCCACTCTGGATCATTGGATGGGCTTACGAAGCAGA
ATGGAGGAAAGATGTCTGACATACTGCTGCAGGCGTCAGTCCAGGTATTGACAGCACACGGT
GCAATGCAGACGATGCGTACCAAGGGGAAGTCACCGAGAAGATGATGTGCAGGCATCCGG
AAGGGGGTGTGGACACCTGCCAGGGTACAGTGGTGGGCCCTGATGTACCAATCTGACCAAGT
GGCATGTGGTGGCATCGTTAGCTGGGCTATGGCTGGGGGCCAGCAGCCAGGAGTAT
ACACCAAGGTCTCAGCCTATCTCAACTGGATCTACAATGTCTGGAAGGCTGAGCTGTAATGCT
GCTGCCCTTGCAGTGCTGGAGCCGTTCCCTGCCCTGCCACCTGGGATCCCCAA
AGTCAGACACAGAGCAAGAGTCCCCTGGTACACCCCTCTGCCACAGCCTCAGCATTCTT
GGAGCAGCAAAGGCCTCAATTCTGTAAGAGACCCCTCGCAGCCCAGAGGCGCCAGAGGAAG
TCAGCAGCCTAGCTGGCCACACTGGTGCTCCAGCATCCAGGGAGAGACACAGCCACT
GAACAAGGTCTCAGGGTATTGCTAAGCCAAGAAGGAACCTTCCCACACTACTGAATGGAAGC
AGGCTGTCTGTAAAAGCCCAGATCACTGTGGCTGGAGAGGAGAAGGAAAGGGTCTGCC
GCCCTGTCCGTCTCACCCATCCCCAAGCCTACTAGAGCAAGAAACCAGTTGTAATATAAAAT
GCACTGCCCTACTGTTGGTATGACTACCGTTACCTACTGTTGTCATTGTTATTACAGCTATGG
CCACTATTATTAAAGAGCTGTGTAACATCTCTGGCAAAAAAA

112/168

FIGURE 112

MLQDPDSQQPLNSLDVKPLRKPRIPMETFRKVGIPIIIALLSLASIIIVVVLKVILDKYFL
CGQPLHFI PRKQLCDGELDCPLGEDEEHCVKSFP EGP AVAVRLSKDRSTLQV LDSATGNWFSA
CFDNFTEAL AETACRQMGYSRAVEIGPDQDLDVVEITENSQELRMRNSSGPCLSGSLVSLHCL
ACGKSLKT PRVVGGE EASV DSWP WQV SIQY DKQH VCGGSILD PHWVL TAAH CFRKHT DVFNWK
VRAGSDKLGSF PSLAVAKIIIIEFNPMYPKDNDIALMKLQFPLTFSGTVRPICL PFFDEELTP
ATPLWIIGWGFTKQNGGKMSDILLQASVQVIDSTRCNADDAYQGEVTEKMMCAGIPEGGVDT
QGDSGGPLMYQSDQWHVVGIVSWGYCGGPSTPGVYTKVSAYLNWIYNVWKAEL

Transmembrane domain:

amino acids 32-53 (typeII)

FIGURE 113

GGCTGGACTGGAACCTCCTGGTCCCAAGTGATCCACCCGCCTCAGCCTCCCAAGGTGCTGTGAT
TATAGGTGTAAGCCACCGTGTCTGGCCTCTGAACAACTTTTCAGCAACTAAAAAGCCACAG
GAGTTGAAC TGCTAGGATTCTGACT**TG**CTGTGGTAGTGCTCCTACTCCTACCTACATT
AAAATCTGTTTTGTTCTCTGTAAC TAGCCTTACCTCCTAACACACAGAGGATCTGTCAC
GTGGCTCTGCCAAACCTGACCTCACTCTGGAACAGAGGTTCTACCCACACCGT
CCCCTCGAAGCCGGGACAGCCTCACCTGCTGGCCTCTCGCTGGAGCAGTGCCTCACCAAC
TGTCTCACGTCTGGAGGCAGTGACTCGGGCAGTGCAGGTAGCTGAGCCTCTGGTAGCTGCGG
CTTCAAGGTGGGCCTTGCCCTGGCGTAGAAGGGAT**TGA**CAAGCCGAAGATTCAAGGCG
ATGGCTCCCACTGCCAGGCATCAGCCTGCTGTAGTCATCACTGCCCTGGGCCAGGACGG
GCCGTGGACACCTGCTCAGAACAGCAGTGGGTGAGACATCACGCTGCCGCCATCTAACCTTT
CATGTCCTGCACATCACCTGATCCATGGCTAATCTGAACCTGTCCCAAGGAACCCAGAGCT
TGAGTGAGCTGTGGCTCAGACCCAGAACAGGGTCTGCTTAGACCACCTGGTTATGTGACAGGA
CTTGCATTCTCCTGGAACATGAGGGAACGCCGGAGGAAAGCAAAGTGGCAGGGAAAGGAACCTG
TGCCAAATTATGGGTAGAAAAGATGGAGGTGTTGGTTATCACAAGGCATCGAGTCTCCTGC
ATTCACTGGACATGTGGGGAAAGGGCTGCCGATGGCGATGACACACTCGGGACTCACCTCTG
GGGCCATCAGACAGCCGTTCCGCCGATCCACGTACAGCTGCTGAAGGGCAACTGCAGGC
CGATGCTCTCATGCCAGGCAGCAGCCAAATCTGCGATCACAGCCAGGGCAGCGTCTG
GGAAGGAGCAAGCAAAGTGACCATTCTCCTCCCTCCTGAGAGGCCCTCTATGT
CCCTACTAAAGCCACCAGCAAGACATAGCTGACAGGGCTAATGGCTCAGTGTGGCCAGGA
GGTCAGCAAGGCCTGAGAGCTGATCAGAACAGGGCTGCTGTGCGAACACGGAAATGCCTCCAGT
AAGCACAGGCTGAAAATCCCCAGGCAAAGGACTGTGTGGCTCAATTAAATCATGTTCTAGT
AATTGGAGCTGTCCCCAAGACCAAAGGAGCTAGAGCTTGGTCAAATGATCTCCAAGGGCCCT
TATACCCCAGGAGACTTGATTGAATTGAAACCCCAAATCCAAACCTAAGAACCCAGGTGCA
TTAAGAACATTGAGCTTGGTGGCTGTAATGCCAACATTGGGAGGCCAGGGCG
GGTAGATCACCTGAGGTCAAGGAGCTGATCAGAACAGCCAGCCTGGCCAACATGGTAAACCCCTGTCTC
TACTAAAAATACAAAAAAACTAGCCAGGCATGGTGGTGTGCTGTATCCCAGCTACTCGGG
AGGCTGAGACAGGAGAATTACTGAAACCTGGGAGGTGAAGGAGGCTGAGACAGGAGAATCACT
TCAGCCTGAGCAACACAGCGAGACTCTGTCAGAAAAAATAAAAAGAATTATGGTTATTT
GTAA

114/168

FIGURE 114

MLWWLVLLLLPTLKVFCISLVTSLYLPNTEDSLWLWPKPDLHSGTRTEVSTHTVPSKPGTAS
PCWPLAGAVPSPTVSRLEALTRAVQVAEPLGSCGFQGGPCPGRRRD

Signal peptide:

amino acids 1-15

FIGURE 115

CAGCAGTGGTCTCTCAGCCTCTCAAAGCAAGGAAAGAGTACTGTGTGCTGAGAGACCATGGC
AAAGAATCCTCCAGAGAATTGTGAAGACTGTACATTCTAAATGCAGAAGCTTTAAATCAA
GAAAATATGTAATCACTTAAGATTGTGGACTGGTGTGTTGGTATCCTGGCCCTAACTCTAAT
TGTCTGTTGGGGAGCAAGCACTCTGGCCGGAGGTACCCAAAAAGCCTATGACATGGA
GCACACTTCTACAGCAATGGAGAGAAGAAGAAGATTACATGGAAATTGATCCTGTGACCAG
AACTGAAATATTAGAAGCGGAATGGCACTGATGAAACATTGGAAGTGCACGACTTTAAAAA
CGGATAACACTGGCATCTACTCGTGGGTCTTCAAAATGTTTATCAAAACTCAGATTAAAGT
GATTCTGAATTTCTGAACCAGAAGAGGAAATAGATGAGAATGAAGAAATTACCAACTTT
CTTGAACAGTCAGTGATTGGTCCCAGCAGAAAAGCCTATTGAAAACCGAGATTCTTAA
AAATTCCAAAATTCTGGAGATTGTGATAACGTGACCATGTATTGGATCAATCCACTCTAAT
ATCAGTTCTGAGTTACAAGACTTGGAGGAGGGAGAAGATCTTCACTTCTGCCAACGA
AAAAAAAGGGATTGAACAAAATGAACAGTGAGGAAGAACTTCCAATAATGACTATACTGAAAATGGAATAGA
ATTTGATCCCAGTCGATGAGAGAGGTTATTGTTGTATTACTGCCGTGAGGCAACCGCTA
TTGCCGCCGCGTCTGTGAACCTTACTAGGCTACTACCCATATCCACTGCTACCAAGGAGG
ACGAGTCATCTGTCGTGTCATCATGCCCTGTAACTGGTGGTGGCCGCATGCTGGGAGGGT
CTAAATAGGAGGTTGAGCTAAATGCTAAACTGCTGGCAACATATAATAATGCATGCTATT
CAATGAATTCTGCCTATGAGGCATCTGGCCCTGGTAGCCAGCTCCAGAATTACTGTAG
GTAATTCTCTTCATGTTCTAATAAAACTTCTACATTACCAAAAAAAAAAAAAAAA

116/168

FIGURE 116

MAKNPPENCEDCHILNAEAFKSKKICKSLKICGLVFGILALTLIVLFWGSKHFWPEVPKKAYD
MEHTFYSNGEKKKIYMEIDPVTTRTEIFRSGNGTDETLEVHDFKNGYTGIYFVGLQKCFIKTQI
KVIPEFSEPEEEEIDENEETTFFEQSVIWVPAEKPIENRDFLKNKILEICDNVTMYWINPT
LISVSELQDFEEEGEDLHFPAKEKKGIEQNEQWVVPQVKVEKTRHARQASEEEELPINDYTENG
IEFDPMELDERGYCCIYCRRGNRYCRRVCEPLLGYYPYCYQGGRVICRVIMPCNWWVARMLGRV

Important features of the protein:

Signal peptide:

amino acids 1-40

Transmembrane domain:

amino acids 25-47 (type II)

N-glycosylation sites.

amino acids 94-97, 180-183

Glycosaminoglycan attachment sites.

amino acids 92-95, 70-73, 85-88, 133-136, 148-151, 192-195, 239-242

N-myristoylation sites.

amino acids 33-38, 95-100, 116-121, 215-220, 272-277

Microbodies C-terminal targeting signal.

amino acids 315-317

Cytochrome c family heme-binding site signature.

amino acids 9-14

FIGURE 117

GAGCTCCCTCAGGAGCGCGTTAGCTTACACCTCGGCAGCAGGAGGGCGGCAGCTCTCGC
AGGCGGCAGGGCGGGCCAGGATATGTCCACCACATGCCAAGTGGTGGCGTCCCTCC
TGTCCATCCTGGGGCTGGCCGGCTGCATCGCGGCCACCGGGATGGACATGTGGAGCACCCAGG
ACCTGTACGACAACCCGTACCTCCGTGTTCCAGTACGAAGGGCTCTGGAGGAGCTGCGTGA
GGCAGAGTTCAGGCTTACCGAATGCAGGCCCTATTCACCATCCTGGGACTTCCAGCCATGC
TGCAGGCAGTGCAGGCCCTGATGATCGTAGGCATCGCCTGGGTGCCATTGGCCTCTGGTAT
CCATCTTGCCCTGAAATGCATCCGCATTGGCAGCATGGAGGACTCTGCCAAAGCCAACATGA
CACTGACCTCCGGGATCATGTTATTGTCTCAGGTCTTGTGCAATTGCTGGAGTGTCTGTGT
TTGCCAACATGCTGGTACTAACTCTGGATGTCCACAGCTAACATGTACACCGGCATGGTGT
GGATGGTGCAGACTGTTCAGACCAGGTACACATTGGTGCAGCTGTGTTGGCTGGGTGCG
CTGGAGGCCTCACACTAATTGGGGGTGTGATGATGTGCATGCCCTGCCGGGCTGGCACCAAG
AAGAAACCAACTACAAAGCCGTTCTTATCATGCCTCAGGCCACAGTGTGCCTACAAGCCTG
GAGGCTCAAGGCCAGCACTGGCTTGGTCCAACACCAAAACAAGAAGATATACGATGGAG
GTGCCCGCACAGAGGACGAGGTACAATCTTATCCTCCAAGCACGACTATGTGTAATGCTCTA
AGACCTCTCAGCACGGCGGAAGAAACTCCGGAGAGCTCACCCAAAAACAAGGAGATCCCA
TCTAGATTCTTCTGCTTTGACTCACAGCTGGAAAGTTAGAAAAGCCTCGATTTCATCTTG
GAGAGGCCAAATGGCTTAGCCTCAGTCTGTCTCTAAATATTCCACCATAAACAGCTGAG
TTATTATGAATTAGAGGCTATAGCTCACATTCAATCCTCTATTCTTTAAATATAA
CTTTCTACTCTGATGAGAGAATGTGGTTTAATCTCTCTCACATTGATGATTTAGACAG
ACTCCCCCTTCCCTCCTAGTCATAAAACCCATTGATGATCTATTCCAGCTTACCCCCAAG
AAAACTTTGAAAGGAAAGAGTAGACCCAAAGATGTTATTCTGCTGTTGAATTGTCTC
CCCACCCCCAACTGGCTAGTAATAAACACTTACTGAAGAAGCAATAAGAGAAAGATATT
TGTAATCTCTCCAGGCCATGATCTCGGTTCTACACTGTGATCTAAAGTTACCAAAACCA
AAGTCATTTCAGTTGAGGCAACCAAACCTTCTACTGCTGTTGACATCTTCTATTACAGC
AACACCATTCTAGGAGTTCTGAGCTCTCCACTGGAGTCCTTCTGCGGGTCAGAAA
TTGTCCTAGATGAATGAGAAAATTATTTTTAATTAAAGTCCTAAATATAGTTAAATAA
ATAATGTTTAGAAAATGATAACTATCTCTGTGAAATAGCCTCACCCCTACATGTGGATAG
AAGGAAATGAAAAATAATTGCTTGACATTGTCTATGGTACTTTGAAAGTCATGCTTAA
GTACAAATTCCATGAAAAGCTCACACCTGTAATCCTAGCACTTGGAGGCTGAGGAGGAAGG
ATCACTTGAGCCCAGAAGTCGAGACTAGCCTGGCAACATGGAGAACGCCCTGTCTCACAAA
ATACAGAGAGAAAAATCAGCCAGTCATGGTGGCATACACCTGTAGTCCCAGCATTCCGGGAG
GCTGAGGTGGAGGATCACTTGAGCCCAGGGAGGTTGGGCTGCAGTGAGCCATGATCACACC
ACTGCACTCCAGCCAGGTGACATAGCGAGATCCTGTCTAAAAAAATAAAATAATGGA
ACACAGCAAGTCCTAGGAAGTAGGTTAAAACTAATTCTTAA

118/168

FIGURE 118

MSTTCQVVAFLLSILGLAGCIAATGMDMWSTQDLYDNPVTSVFQYEGLWRSCVRQSSGFTEC
R PYFTILGLPAMLQAVRALMIVGIVLGAIGLLVSIFALKCIRIGSMEDSAKANMLTSGIMFI
VSGLCIAIGVSVFANMLVTNFWMSTANMYTGMGGMVQTVQTRYTFGAALFVGVWAGGLTLIGG
VMMCIACRGLAPEETNYKAVSYHASGHSVAYKPGGFKA STGFGSNTKNKKIYDGGARTEDEVQ
SYPSKHDYV

Signal peptide:

amino acids 1-23

Transmembrane domains:

amino acids 81-100, 121-141, 173-194

FIGURE 119

GGAAAAACTGTTCTTCTGTGGCACAGAGAACCTGCTCAAAGCAGAAGTAGCAGTTCCGG
AGTCCAGCTGGCTAAACTCATCCCAGAGGATAATGGCAACCCATGCCTTAGAAATCGCTGGG
CTGTTCTGGTGGTGGATGGTGGCACAGTGGCTGTCAGTGTGATGCCTCAGTGGAGA
GTGTCGGCCTTCATTGAAAACAACATCGTGGTTTGAAAACCTCTGGGAAGGACTGTGGATG
AATTGCGTGAGGCAGGCTAACATCAGGATGCAGTGCAAAATCTATGATTCCCTGCTGGCTCTT
TCTCCGGACCTACAGGCAGCCAGAGGACTGATGTGCTGCTCCGTGATGTCCTCTGGCT
TTCATGATGGCCATCCTGGCATGAAATGCACCCAGGTGCACGGGGACAATGAGAAGGTGAAG
GCTCACATTCTGCTGACGGCTGGAATCATCTCATCACGGCATGGTGGTGCATCCCT
GTGAGCTGGGTTGCCAATGCCATCATCAGAGATTCTATAACTCAATAGTGAATGTTGCCAA
AACAGTGAGCTGGAGAAGCTCTACTTAGGATGGACCACGGCACTGGTGCATTGTTGGA
GGAGCTCTGTTCTGCTGCGTTTGCAACGAAAAGAGCAGTAGCTACAGATACTCGATA
CCTTCCCATCGCACACCCAAAAAGTTATCACACCGAAAGAAGTCACCGAGCGTCTACTCC
AGAAGTCAGTATGTGTAGTTGTATGTTTTAACTTACTATAAGCCATGCAAATGACA
AAAATCTATATTACTTCTAAAATGGACCCAAAGAAACTTGTATTACTGTTCTTAACG
CTAATCTTAATTACAGGAACGTGCATCAGCTATTATGATTCTATAAGCTATTCAGCAGAA
TGAGATATTAAACCCAAATGCTTGATTGTTCTAGAAAGTATAGTAATTGTTCTAAGGTGG
TTCAAGCATCTACTCTTTATCATTACTTCAAAATGACATTGCTAAAGACTGCATTATTT
ACTACTGTAATTCTCCACGACATAGCATTATGTACATAGATGAGTGTAAACATTATCTCA
CATAGAGACATGCTTATATGGTTTATTAAAATGAAATGCCAGTCCATTACACTGAATAAAAT
AGAACTCAACTATTGCTTTCAGGGAAATCATGGTAGGGTTGAAGAAGGTTACTATTG
TTAAAAACAGCTTAGGGATTAAATGTCCTCCATTATAATGAAGATTAAAATGAAGGCTTAA
TCAGCATTGTAAGGAAATTGAATGGCTTCTGATATGCTGTTTAGCCTAGGAGTTAGAA
ATCCTAACTCTTATCCTCTCCAGAGGCTTTCTGTGATTAAATTAAACATT
TTTAAAACGCAGATATTGTCAGGGCTTGCATTCAAATGCTTCCAGGGCTATACTC
AGAAGAAAGATAAAAGTGTGATCTAAGAAAAGTGTAGGTTAGGAAAGTGAATAATT
GTTTTGTATTGAGAAGAAGAATGATGCATTGACAAGAAATCATATATGTATGGATATATT
TAATAAGTATTGAGTACAGACTTGAGGTTCATCAATATAAAAGAGCAGAAAATAT
GTCTGGTTTCATTGCTTACCAAAAAACAAACAACAAAAAGTTGTCCTTGAGAACCTC
ACCTGCTCCTATGTGGTACCTGAGTCAAATTGTCATTGTTCTGTGAAAAATAATT
CTTCTGTACCATTTCTGTTAGTTACTAAAATCTGAAATACTGTATTCTGTTATT
CCAAATTGATGAAACTGACAATCCAATTGAAAGTTGTCGACGTCTGTAGCTAAAT
GAATGTGTTCTATTGCTTATACATTATAAAATTGTACATTCTAATT

120/168

FIGURE 120

MATHALEIAGLFLGGVGMVGTAVTVMPQWRVSAFIENNIVVFENFWEGLWMNCVRQANIRMQ
CKIYDSLLALSPDLQAARGLMCAASVMSFLAFMAILGMKCTRGTGDNEKVKAHILLTAGIIF
IITGMVVLIPVSWANAIIRDFYNSIVNVAQKRELGEALYLGWTALVLIVGGALFCCVFCCN
EKSSSYRYSIPSHRTTQKSYHTGKKSPSVYSRSQYV

Signal peptide:

amino acids 1-17

Transmembrane domains:

amino acids 82-101, 118-145, 164-188

121/168

FIGURE 121

GGAGAGAGGCGCGCGGGTGAAAGGCGCATTGATGCAGCCTGCGGCGGCCTCGGAGCGCGGGCG
AGCCAGACGCTGACCACGTTCTCCTCGGTCTCCTCCGCCTCCAGCTCCGCGCTGCCCGC
AGCCGGAGCC**ATG**CGACCCAGGGCCCCGCCGCCTCCCGCAGCGGCTCCGCGGCCCTGC
TGCTCCTGCTGCTGCAGCTGCCGCCGTCAGCGCCTCTGAGATCCCCAAGGGGAAGCAAA
AGGCGCAGCTCCGGCAGAGGGAGGTGGACCTGTATAATGGAATGTGCTTACAAGGGCCAG
CAGGAGTGCCTGGTCGAGACGGGAGCCCTGGGGCCAATGTTATTCCGGGTACACCTGGATCC
CAGGTGGGATGGATTCAAAGGAGAAAAGGGGAATGTCAGGGAAAGCTTGAGGAGTCCT
GGACACCCAACTACAAGCAGTGTTCATGGAGTTCAATTGGAATTATGGCATAGATCTGGGAAAA
TTGCGGAGTGTACATTACAAAGATGCAGTTCAAATAGTGCCTAAGAGTTTGTTCAGTGGCT
CACTCGGCTAAATGCAGAAATGCATGCTGTCAGCGTTGGTATTCACATTCAATGGAGCTG
AATGTTCAAGGACCTCTCCCATTGAAGCTATAATTATTGGACCAAGGAAGCCCTGAAATGA
ATTCAACAATTAATATTCACTCGCACTTCTGTGGAAGGACTTGTGAAGGAATTGGTGTG
GATTAGTGGATGTTGCTATCTGGGTTGGCACTTGTTCAGATTACCCAAAAGGAGATGCTCTA
CTGGATGGAATTCACTTCTCGCATCATTATTGAAGAACTACCAAA**TAA**ATGCTTTAATT
CATTTGCTACCTTTTTATTATGCCTGGAATGGTTCACTAAATGACATTAAATAAG
TTTATGTATACATCTGAATGAAAAGCAAAGCTAAATATGTTACAGACCAAGTGTGATTCA
CACTGTTTAAATCTAGCATTATTCAATTGCTCAATCAAAAGGGTTCAATATTTTT
TAGTTGGTTAGAATACTTCTTCATAGTCACATTCTCTCAACCTATAATTGGAATATTGTTG
TGGCTTTGTTCTCTAGTATAGCATTAAAAAAATATAAAAGCTACCAATTGTT
TACAATTGAAATGTTAAGAATTCTATCTGTTAAATAAAATTATTCCAACA

122/168

FIGURE 122

MRPQGPAA SPQR LRG LLLL LQLP APSS ASEIPKGKQKAQLRQREVVDLYNGMCLQGPAGVP
GRDGSPGANV I PGT PGIPGRDGFKGEKGECLRESFEESWT PNYKQCSWSSLNYGIDLGKIAEC
TFTKMR SNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGPLPIEAIYLDQGSPEMNSTI
NIHRTSSVEGLCEGIGAGLVDV A I WVGTCSDYPKG DASTGWNSVSRIIIEELPK

Signal peptide:

amino acids 1-30

Transmembrane domain:

amino acids 195-217

123/168

FIGURE 123

GCTGAGCGTGTGCGCGGTACGGGGCTCTCCTGCCTCTGGGCTCCAACGCAGCTCTGTGGCTG
AACTGGGTGCTCATCACGGAACTGCTGGCTATGGAATACAGATGTGGCAGCTCAGGTAGCC
CCAAATTGCCTGGAAGAATACATCATGTTTCGATAAGAAGAAATTGTAGGATCCAGTTTT
TTTTAACCGCCCCCTCCCCACCCCCAAAAAACTGTAAGAGATGCAAAACGTAATATCCAT
GAAGATCCTATTACCTAGGAAGATTGTATGTTGCTGCGAATGCGGTGTTGGGATTATT
GTTCTGGAGTGTCTGCGTGGCTGGCAAAGAATAATGTTCCAAATCGGTCCATCTCCCAAG
GGGTCCAATTTCCTGGGTGTCAGCGAGCCCTGACTCACTACAGTGCAGCTGACAGGGG
CTGTCATGCAACTGGCCCTAACGCAAAGCAAAAGACCTAACGGACGACCTTGAAACAATACAA
AGG**ATGG**TTCAATGTAATTAGGCTACTGAGCGGATCAGCTGAGCTGGTTATAGCCCCC
ACTGCTTACTGACAATGCTTCTTGCAGCGAGGATGCCCTAACGGCTGTAGGTGTGAA
GGCAAAATGGTATATTGTGAATCTCAGAAATTACAGGAGATACCCCTCAAGTATATCTGCTGGT
TGCTTAGGTTGTCCTCGTATAACAGCCTCAAAACTTAAGTATAATCAATTAAAGGG
CTCAACCAGCTCACCTGGCTATACCTGACCATAACCATAACGCAATTGACGAAAATGCT
TTAATGGAATACGCAACTCAAAGAGCTGATTCTTAGTTCCAATAGAATCTCCTATTTCTT
AACAAATACCTTCAGACCTGTGACAAATTACGGAACCTGGATCTGCTTACAGCTGCAT
TCTCTGGGATCTGAACAGTTGGGGCTTGCGGAAGCTGCTGAGTTACATTACGGTCTAAC
TCCCTGAGAACCATCCCTGTGCGAATTCCAAGACTGCCAACCTGGAACCTTGGACCTG
GGATATAACCGGATCCGAAGTTAGCCAGGAATGTCTTGCTGGCATGACTCAAAGAA
CTTCACCTGGAGCACAAATCAATTTCAGCTCAACCTGGCCCTTTCCAAGGTTGGTCAGC
CTTCAGAACCTTACTTGCAGTGGAAATAAAACTAGTGTCAAGGACAGACCATGTCCTGGACC
TGGAGCTCCTTACAAAGGCTGATTATCAGGCAATGAGATCGAAGCTTCAGTGGACCCAGT
GTTTCCAGTGTGTCCTGAATCTGCAGCGCCTCAACCTGGATTCCAACAAGCTCACATTATT
GGTCAAGAGATTGGATTCTGGATATCCCTCAATGACATCAGTCTGCTGGGAATATATGG
GAATGCAGCAGAAATTGGCTCCCTGTAAACTGGCTGAAAAGTTAAAGGCTAAGGGAG
AAATACAATTATCTGTGCCAGTCCAAAGAGCTGCAAGGAGTAATGTGATCGATGCAGTGAAG
AACTACAGCATCTGTGGAAAAGTACTACAGAGAGGTTGATCTGCCAGGGCTCTCCAAAG
CCGACGTTAACGCCAAGCTCCCCAGGCCAGCATGAGAGCAAAACCCCTTGCCCCCGACG
GTGGGAGCCACAGAGCCGGCCAGAGACCGATGCTGACGCCAGCACATCTCTTCCATAAA
ATCATCGCGGGCAGCGTGGCGCTTTCTGTCGTGCTCATCCTGCTGGTTATCTACGTG
TCATGGAAGCGGTACCCCTGCGAGCATGAAGCAGCTGCGAGCGCTCCCTCATGCGAAGGCAC
AGGAAAAAGAAAAGACAGTCCCTAAAGCAAATGACTCCCAGCACCCAGGAATTATGTAGAT
TATAAACCCACCAACACGGAGACCAGCGAGATGCTGCTGAATGGGACGGGACCTGCACCTAT
AAACAAATCGGGCTCCAGGGAGTGTGAGGTA**TGA**ACCATTGTGATAAAAGAGCTTTAAAGC
TGGGAAATAAGTGGTGTCTTATTGAACCTGGTGAATCAAGGGAACCGATGCCCTC
CCCTCCCTCTCCCTCACTTGGTGGCAAGATCCTCCTGTCGTTTAGTGCATTATA
ATACTGGTCATTTCTCTCATACATAATCAACCCATTGAAATTAAATACCAACATCAATGT
GAAGCTTGAACCTCGGTTAATATAACCTATTGTATAAGACCCCTTACTGATTCCATTAAAT
GTCGCATTGTTTAAGATAAAACTTCTTCATAGGTAAAAAAAAAA

FIGURE 124

MGFNVIRLLSGSAVALVIAPTVLLTMLSSAERGCPKGCRCEGMVYCESQKLQEIPSSISAGC
LGSLRYNSLQKLKYNQFKGLNQLTWLYLDHNNHISNIIDENAFNGIRRLKELILSSNRISYFLN
NTFRPVTNLRNLDLSYNQLHSLGSEQFRGLRKLSSLHRSNSLRTIPVRI FQDCRNLELLDLG
YNRIRSLARNVFAGMIRLKELHLEHNQFSKLNLAFFPRLVSLQNLYLQWNKISVIGQTMSWTW
SSLQRLDLSGNEIEAFSGPSVFQCVPNLQRLNLDNSNKLTFIGQEILDWSISLNDISLAGNIWE
CSRNICSLVNLKSFKGLRENTIICASPKELQGVNVIDAVKNYSICGKSTTERFDLARALPKP
TFKPKLPRPKHESKPLPPTVGATEPGPETDADAEHISFHKI IAGSVALFLSVLVILLVIYVS
WKRYPASMKQLQQRSLMRRHRKKRQSLKQMTPSTQE FYVDYKPTNTETSEMLLN GTGPCTYN
KSGSRECEV

Important features of the protein:

Signal peptide:

amino acids 1-33

Transmembrane domain:

amino acids 420-442

N-glycosylation sites.

amino acids 126-129, 357-360, 496-499, 504-507

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 465-468

Tyrosine kinase phosphorylation site.

amino acids 136-142

N-myristoylation sites.

amino acids 11-16, 33-38, 245-250, 332-337, 497-502, 507-512

125/168

FIGURE 125

CCGTTATCGTCTTGCCTACTGCTGAATGTCCGTCCCGAGGAGGAGGAGGCTTTGCCGC
TGACCCAGAGATGGCCCCGAGCGAGCAAATTCTACTGTCCGGCTGCAGGCTACCGTGGCCG
AGCTAGCAACCTTCCCTGGATCTCACAAAAACTCGACTCCAAATGCAAGGAGAAGCAGCTC
TTGCTCGGTGGAGACGGTGCAAGAGAATCTGCCCCCTATAGGGGAATGGTGCACAGCCC
TAGGGATCATTGAAGAGGAAGGCTTCTAAAGCTTGGCAAGGAGTGACACCCGCCATTACA
GACACGTAGTGTATTCTGGAGGTGAATGGTCACATATGAACATCTCCGAGAGGTTGTGTTG
GCAAAAGTGAAGATGAGCATTATCCCCTTGGAAATCAGTCATTGGAGGGATGATGGCTGGTG
TTATTGGCCAGTTTAGCCAATCCAAC TGACCTAGTGAAGGTTCAAGTGCACATGGAAAGGAA
AAAGGAAACTGGAAGGAAACCATTGCGATTCGTGGTACATCATGCATTGCAAAATCT
TAGCTGAAGGAGGAATACGAGGGCTTGGCAGGCTGGTACCCAATATAACAAAGAGCAGCAC
TGGTGAATATGGGAGATTAACCACTTATGATACAGTGAACACTACTTGGTATTGAATACAC
CACTTGAGGACAATATCATGACTCACGGTTATCAAGTTATGTTCTGGACTGGTAGCTCTA
TTCTGGAACACCAGCCGATGTCATCAAAAGCAGAATAATGAATCAACCACGAGATAACAAG
GAAGGGGACTTTGTATAAATCATCGACTGACTGCTTGATTCAAGGCTGTTCAAGGTGAAGGAT
TCATGAGTCTATATAAAGGCTTTACCATCTGGCTGAGAATGACCCCTGGTCAATGGTGT
TCTGGCTTACTTATGAAAAAATCAGAGAGATGAGTGGAGTCAGTCCATTTAA

126/168

FIGURE 126

MSVPEEEERLLPLTQRWPRASKFLLSGCAATVAELATFPLDLTKTRLQMGEAALARLGDGAR
ESAPYRGMVRTALGIIEEGFLKLWQGVTPAIYRHVVYSGGRMVTYEHLREVVFGKSEDEHYP
LWKSVIGGMMAGVIGQFLANPTDLVKVQMQMEGKRKLEGKPLRFRGVHHAFAKILAEGGIRGL
WAGWVPNIQRAALVNMGDLTTYDTVKHYLVLNTPLEDNIMTHGLSSLCGLVASICLTPADVI
KSRIMNQPRDKQGRGLLYKSSTDCLIQAVQGEGFMSLYKGFLPSWLRMTPWSMVFWLTYEKIR
EMSGVSPF

Transmembrane domains:

amino acids 25-38, 130-147, 233-248

127/168

FIGURE 127

CGCGGATCGGACCAAGCAGGTGGCGGCGGCGAGGAGAGCGGCCGGCGTCAGCTCCTCG
ACCCCCGTGTCGGGCTAGTCAGCGAGGCGGACGGCGGTGGGCCATGGCCAGGCCGGC
ATGGAGCGGTGGCGACCGGCTGGCGCTGGTACGGGGCCTCGGGGGCATGGCGCGGC
GTGGCCCGGGCCCTGGTCCAGCAGGGACTGAAGGTGGTGGCTGCGCCGCAGTGGCAAC
ATCGAGGAGCTGGCTGTAATGTAAGAGTCAGGCTACCCCGGACTTTGATCCCCTACAGA
TGTGACCTATCAAATGAAGAGGACATCCTCTCCATGTTCTCAGCTATCCGTTCTCAGCACAGC
GGTAGACATCTGCATCAACAATGCTGGCTGGCCGGCTGACACCCCTGCTCTCAGGCAGC
ACCAGTGGTTGGAAGGACATGTTCAATGTGAACGTGCTGGCCCTCAGCATCTGCACACGGAA
GCCTACCAGTCCATGAAGGAGCGGAATGTGGACGATGGCACATCATTAAACATCAATAGCATG
TCTGGCCACCGAGTGTACCCCTGTCTGTGACCCACTTCTATAGTGCCACCAAGTATGCCGTC
ACTGCGCTGACAGAGGGACTGAGGCAAGAGCTCGGGAGGCCAGACCCACATCCGAGGCCACG
TGCATCTCTCCAGGTGGTGGAGACACAATTGCCCTCAAACCTCCACGACAAGGACCTGAG
AAGGCAGCTGCCACCTATGAGCAAATGAAGTGTCTCAAACCCGAGGATGTGGCGAGGCTGTT
ATCTACGTCTCAGCACCCCCGACACATCCAGATTGGAGACATCCAGATGAGGCCACGGAG
CAGGTGACCTAGTGACTGTGGGAGCTCCTCCTCCACCCCTCATGGCTGCCTCCTG
CCTCTGGATTTAGGTGTTGATTCTGGATCACGGGATACCACCTCCTGTCCACACCCGACC
AGGGGCTAGAAAATTGTTGAGATTATATCATCTTGTCAAATTGCTTCAGTTGAAATG
TGAAAAATGGCTGGGAAAGGAGGTGGTGTCCCTAATTGTTACTTGTAACTTGTCTTG
TGCCCCCTGGCACTTGGCCTTGTCTGCTCTCAGTGTCTCCCTTGACATGGAAAGGAGTT
GTGGCCAAAATCCCCATCTCTGCACCTCAACGTCTGGCTCAGGGCTGGGTGGCAGAGG
GAGGCCTCACCTATATCTGTGTTATCCAGGGCTCCAGACTTCCCTCTGCCTGCC
ACTGCACCCCTCTCCCCCTATCTATCTCCTCTCGGCTCCCAGCCAGTCTGGCTCTGT
CCCCCTCTGGGTCACTCCACTCTGACTATGGCAGCAGAACACCAGGGCTGGC
CCAGTGGATTCATGGTGATCATTAAAAAGAAAAATCGCAACCAAAAAAA

128/168

FIGURE 128

MARPGMERWRDRLALVTGASGGIGAAVARALVQQGLKVVG CARTVGNIEELAAECKSAGYPGT
LIPYRCDSLNEEDILSMFSAIRSQHSGVDICINNAGLARPDTLLSGSTSGWKDMFNVNLALS
ICTREAYQSMKERNVDDGHIININMSGHRVLPLSVTHFYSATKYAVTALTEGLRQELREAQT
HIRATCISPGVETQFAFKLHDKDPEKAAATYEQMKCLKPEDVAEAVIYVLSTPAHIQIGDIQ
MRPTEQVT

Important features of the protein:

Signal peptide:

amino acids 1-17

N-myristoylation sites.

amino acids 18-24, 21-27, 22-28, 24-30, 40-46, 90-96, 109-115,
199-205

Short-chain alcohol dehydrogenase.

amino acids 30-42, 104-114

129/168

FIGURE 129

AACTTCTACATGGGCCTCCTGCTGCTGGTGCTCTCCTCAGCCTCCTGCCGGTGGCCTACACC
ATCATGTCCTCCCACCCCTCTTGACTGCGGGCCGTTCAAGGTGCAGAGTCTCAGTTGCCCGG
GAGCACCTCCCCTCCCGAGGCAGTCTGCTCAGAGGGCCTCGGCCAGAATTCCAGTTCTGGTT
TCATGCCAGCCTGTAAAAGGCCATGGAACCTTGGGTGAATCACCGATGCCATTAAGAGGGTT
TTCTGCCAGGATGAAATGTTAGGTCGTTCTGTGCTGCGCTGTTCAATTCAAGTAGCCACCAAG
CCACCTGTGGCGTTGAGTGCTGAATGAAGGAACGTGAGAAAATTAAATTCTCATGTATT
CTCATTATTATTAAATTAACTGATAGTTGACATATTGGGGTACATGTGATATTGG
ATACATGTATACAATATAATGATCAAATCAGGGTAACACTGGGATATCCATCACATCAAACAT
TTATTTTTATTCTTTAGACAGAGTCTCACTCTGTCACCCAGGCTGGAGTGCAGTGGTGCC
ATCTCAGCTTACTGCAACCTCTGCCAGGTTCAAGCGATTCTCATGCCCTCACCTCCAA
GTAGCTGGACTACAGGCATGCACCACAATGCCAACTAATTGTATTAGAGACG
GGGTTTGCCATGTTGCCAGGCTGGCCTGAACCTGCCCTCAAACAATCCACTGCCCTCG
GCCCTCCAAAGTGTATGATTACAGGCAGTGCCTGGCCTAAACATTTATCTTT
CTTGTGTTGGAACTTGAAATTATAACATGAATTATTGTTAAGTGTACATCTCCCTGCTGTG
CTATGGAACACTGGACTTCTCCCTCTATCTAACTGTATATTGTACCAAGTTAACCAACCGT
ACTTCATCCCCACTCCTCTATCCTCCAAACCTCTGATCACCTCATCTACTCTACCTC
CATGAGATCCACTTTAGCTCCACATGTGAGTAAGAAAATGCAATATTGTCTTCTGTG
CCTGGCTTATTCACTTAACATAATGACTCCTGTTCCATGTTGCTGCAAATGACAGGA
TTTCGTTCTTAATTCAATTAAAATAACCACACATGGCAAAAA

130/168

FIGURE 130

MGLLLLVLFLSLLPVAYTIMSLPPSFDCGPFRCRVSVAREHLPGRGSLLRGPRPRI PVLVSCQ
PVKGHGTLGESPMPFKRVFCQDGTVRSFCVCAVFSSHQPPVAVECLK

Important features of the protein:

Signal peptide:

amino acids 1-18

N-myristoylation site.

amino acids 86-92

Zinc carboxypeptidases, zinc-binding region 2 signature.

amino acids 68-79

FIGURE 131

TTCTGAAGTAACGGAAGCTACCTGTATAAAGACCTAACACTGCTGACCATGATCAGCGCAG
CCTGGAGCATCTCCTCATCGGGACTAAAATTGGGCTGTCCTCAAGTAGCACCTCTATCAG
TTATGGCTAAATCCTGTCCATCTGTGTGCGATGCGGGTTCTTACTGTAATGATC
GCTTCTGACATCCATTCCAACAGGAATACCAGAGGATGCTACAACCTCTACCTTCAGAAC
ACCAAATAATAATGCTGGGATTCCCTCAGATTGAAAAACTTGCTGAAAGTAGAAAGAAATAT
ACCTATACCACACAGTTAGATGAATTCCCTACCAACCTCCAAAGTATGTAAGAGTTAC
ATTTGCAAGAAAATAACATAAGGACTATCACTTATGATTCACTTCAAAAATTCCCTATCTGG
AAGAATTACATTTAGATGACAACCTCTGTCTGAGTTAGCATAGAAGAGGGAGCATTCCGAG
ACAGCAACTATCTCCGACTGCTTTCTGTCCGTAATCACCTAGCACAATTCCCTGGGGTT
TGCCCAGGACTATAGAAGAACTACGCTGGATGATAATCGATATCCACTATTCATCACCAT
CTCTCAAGGTCTCACTAGTCTAAACGCCTGGTTCTAGATGAAACCTGTTGAACAATCATG
GTTAGGTGACAAAGTTTCTAACCTAGTTAATTGACAGAGCTGTCCTGGCGGAATT
CCCTGACTGCTGCACCAGTAAACCTTCCAGGCACAAACCTGAGGAAGCTTATCTCAAGATA
ACCACATCAATGGGTGCCCAAATGCTTTCTTATCTAAGGCAGCTCTATCGACTGGATA
TGTCCAATAATAACCTAAGTAATTACCTCAGGGTATCTTGATGATTGGACAATATAACAC
AACTGATTCTCGCAACAATCCCTGGTATTGCGGGTGCAAGATGAAATGGGTACGTGACTGGT
TACAATCACTACCTGTGAAGGTCAACGTGCGTGGCTCATGTGCCAAGCCCCAGAAAAGGTT
GTGGGATGGCTATTAAGGATCTCAATGCAGAACTGTTGATTGTAAGGACAGTGGATTGAA
GCACCATTCAAGATAACCAACTGCAATACCCACACAGTGTATCCTGCCAAGGACAGTGGCCAG
CTCCAGTGACCAAACAGCCAGATATTAAGAACCCCAAGCTCACTAAGGATCAACAAACCACAG
GGAGTCCCTCAAGAAAAACAATTACAATTACTGTGAAGTCTGTCACCTCTGATACCATTATA
TCTCTGGAAACTTGCTCTACCTATGACTGCTTGAGACTCAGCTGGCTAAACTGGGCCATA
GCCCGGCATTGGATCTATAACAGAAACAATTGTAACAGGGGAACGCAGTGAGTACTGGTCA
CAGCCCTGGAGCCTGATTCCCTATAAAAGTATGCATGGTCCCATGGAAACCAGCAACCTCT
ACCTATTGATGAAACTCCTGTTGTATTGAGACTGAAACTGCACCCCTCGAATGTACAACC
CTACAACCACCCCTCAATCGAGAGCAAGAGAAAGAACCTTACAAAAACCCAAATTACCTTGG
CTGCCATCATTGGTGGGCTGTGGCCCTGGTTACCATTGCCCTCTGCTTAGTGTGTTGGT
ATGTTCATAGGAATGGATCGCTTCAAGGAACGTGCAATAGCAAAGGGAGGAGAAGAA
AGGATGACTATGCAGAAGCTGGCACTAAGAAGGACAACCTATCCTGGAAATCAGGGAAACTT
CTTTCAAGATGTTACCAATAAGCAATGAACCCATCTCGAAGGAGGAGTTGTAATACACACCA
TATTCCTCCTAATGGAATGAATCTGTACAAAAACAATCACAGTGAAAGCAGTAGTAACCGAA
GCTACAGAGACAGTGGTATTCCAGACTCAGATCACTCACACTCATTGATGCTGAAGGACTCACA
GCAGACTTGTGTTGGTTTTAACCTAAGGGAGGTGATGGT

FIGURE 132

MISAAWSIFLIGTKIGLFLQVAPLSVMAKSCPSVCRC DAGFIYCNDRFLTSIPTGIPEDATTLYLQNNQINNAGIPSDLKNLLKVERIYLYHNSLDEFPTNLPKYVKEHLQENNIRTITYDSLKI PYLEELHLDNSVSAVSIEEGAFRDSNYLRLLFLSRNHLS TI PWGLPRTIEELRLDDNRISTI SSPLQGLTSLKRLVLDGNLLNNHGLDKVFFNLVNLTELSLVRNSLTAAPVNLPGTNLRKL YLQDNHINRVPPNAFSYLRQLYRLDMSNNNLSNLPQGIFDDLDNITQLI LRNNPWYCGCKMKW VRDWLQSLPVKVNVRGLMCQAPEKVRGMAIKDLNAELFDCKDSGIVSTI QT TAIPNTVYPAQ GQWPAPVTKQPDIKNPKLTKDQQTGSPSRKTITITVKS VTS DTI HISWKLALPMTALRLSWL KLGHSPA FG SITETIVTGERSEYLVTALEPDSPYKVC MVPMETSNLYLFDETPVCIETETAPL RMYNPTTLLNREQEKEPYKNPNLPLAAIIGGAVALVTI ALLALVCWYVHRNGSLFSRNCAYS K GRRRKDDYAEAGTKKD NSILEIRETSFQMLPISNEPISKEE FVIHTI FPPNGMNLYKNNHSES SSNRSYRDSGIPDSDHSHS

Important features of the protein:

Signal peptide:

amino acids 1-28

Transmembrane domain:

amino acids 531-552

N-glycosylation sites.

amino acids 226-229, 282-285, 296-299, 555-558, 626-629, 633-636

Tyrosine kinase phosphorylation site.

amino acids 515-522

N-myristoylation sites.

amino acids 12-17, 172-177, 208-213, 359-364, 534-539, 556-561,

640-645

Amidation site.

amino acids 567-570

Leucine zipper pattern.

amino acids 159-180

Phospholipase A2 aspartic acid active site.

amino acids 34-44

FIGURE 133

CCGTCATCCCCCTGCAGCCACCCCTCCAGAGTCCTTGCCCCAGGCCACCCAGGCTTCTGG
CAGCCCTGCCGGGCCACTTGTCTTCATGTCTGCCAGGGGAGGTGGGAAGGAGGTGGGAGGAG
GGCGTGCAGAGGCAGTCTGGCTTGGCCAGAGCTCAGGGTGCTGAGCGTGTGACCAGCAGTGA
GCAGAGGCCGGCATGCCAGCCTGGGCTGCTCCTGCTCTTACTGACAGCACTGCCACC
GCTGTGGTCTCCTCACTGCCCTGGACACTGCTGAAAGTAAAGCCACCATTGCAGACCT
GATCCTGTCTGCGCTGGAGAGAGCCACCGTCTCCTAGAACAGAGGCTGCCTGAAATCAACCT
GGATGGCATGGTGGGGTCCGAGTGCTGGAAGAGCAGCTAAAAGTGTCCGGAGAAGTGGC
CCAGGAGCCCCCTGCTGCAGCCGCTGAGCCTGCGGTGGGATGCTGGGGAGAAGCTGGAGGC
TGCCATCCAGAGATCCCTCCACTACCTCAAGCTGAGTGATCCCAAGTACCTAACGAGAGTCCA
GCTGACCCCTCCAGCCGGTTTGGAAAGCTCCCACATGCCTGGATCCACACTGATGCCTCCTT
GGTGTACCCCACGTTGGGCCCCAGGACTCATTCTCAGAGGAGAGAAGTGACGTGTGCCTGGT
GCAGCTGCTGGAACCGGGACGGACAGCAGCGAGCCCTGCGGCCTCTCAGACCTCTGCAGGAG
CCTCATGACCAAGCCCGCTGCTCAGGCTACTGCCTGTCACCAACTGCTCTTCTCCTCTG
GGCCAGAATGAGGGGATGCACACAGGGACCCTCAACAGAGCCAGGACTATATCAACCTCTT
CTGCGCCAACATGATGGACTTGAACCGCAGAGCTGAGGCCATGGATACGCCTACCCCTACCG
GGACATCTTCATGGAAAACATCATGTTCTGTGGAATGGCGGCTCTCGACTTCTACAAGCT
CCGGTGGCTGGAGGCCATTCTCAGCTGGCAGAAACAGCAGGAAGGATGCTCGGGAGCCTGA
TGCTGAAGATGAAGAATTATCTAAAGCTATTCAATATCAGCAGCATTTCGAGGAGAGTGAA
GAGGCGAGAAAAACAATTCCAGATTCTCGCTCTGGCTCAGGCTGGAGTACAGTGGCGCAA
TCTCGGCTCACTGCAACCTTGCCTCCTGGTTCAAGCAATTCTCTGCCTCATCCTCCGAG
TAGCTGGACTACAGGAGCGGCCACCATACCTGGCTAATTTTATATTTTTAGTAGAGAC
AGGGTTTCATCATGTTGCTCATGCTGGCTCGAACCTGATCTCAAGAGATCCGCCACCTC
AGGCTCCAAAGTGTGGGATTATAGGTGTGAGCCACCGTGTGGCTGAAAGCACTTCAA
GAGACTGTGTTGAATAAGGGCCAAGGTTCTGCCACCCAGCACTCATGGGGCTCTCTCCCC
TAGATGGCTGCTCCTCCCACAACACAGCCACAGCAGTGGCAGCCCTGGGTGGCTCCTATACA
TCCTGGCAGAATACCCCCCAGCAAACAGAGAGGCCACACCCATCCACACCGCCACCAAGCA
GCCGCTGAGACGGACGGTTCCATGCCAGCTGCCCTGGAGGAGGAACAGACCCCTTAGTCCTCA
TCCCTTAGATCCTGGAGGGCACGGATCACATCCTGGGAAGAAGGCATCTGGAGGATAAGCAA
GCCACCCGACACCCAAATCTTGAAGCCCTGAGTAGGCAGGGCAGGGTAGGTGGGGCCGGG
AGGGACCCAGGTGTGAACGGATGAATAAGTCAACTGCAACTGAACTGAAAAAA

134/168

FIGURE 134

MSARGRWEGGGRRACRGSLGLARAQGAERVTSSERQPAMASLGLLLLLTLAPPLWSSSLPG
LDTAESKATIADLILSALERATVFLEQRLPEINLDGMGVVRVLEQLKSVREKWAQEPLLQPL
SLRVGMLGEKLEAAIQRSLHYLKLSDPKYLREFQLTLQPGFWKLPHAWIHTDASLVYPTFGPQ
DSFSEERSDVCLVQLLGTGTDSEPCGLSDLRSLMTKPGCGYCLSHQLLFFLWARMRGCTQ
GPLQQSQDYINLFCANMMDILNRRAEAIGYAYPTRDIFMENIMFCGMGGFSDFYKLRWLEAILS
WQKQQEGCFGEPDAEDEELSKAIQYQQHFSRRVKRREKQFPDSRSVAQAGVQWRNLGSLQPLP
PGFKQFSCLILPSSWDYRSVPPYLANFYIFLVETGFHHVAHAGLELLISRDPPTSGSQSVGL

Important features of the protein:

Signal peptide:

amino acids 1-26

Transmembrane domain:

amino acids 39-56

Tyrosine kinase phosphorylation sites.

amino acids 149-156, 274-282

N-myristoylation sites.

amino acids 10-16, 20-26, 63-69, 208-214

Amidation site.

amino acids 10-14

Glycoprotein hormones beta chain signature 1.

amino acids 230-237

FIGURE 135

GGTCTGAGTGCAGAGCTGCTGTCATGGCGGCCGCTCTGTGGGCTTCTTCCCCTGCTGC
TGCTGCTGCTATCGGGGGATGTCCAGAGCTCGGAGGTGCCCGGGCTGCTGCTGAGGGATCGG
GAGGGAGTGGGTCGGCATAGGAGATCGCTCAAGATTGAGGGCGTGCAGTTGTTCCAGGGG
TGAAAGCCTCAGGACTGGATCTGGCGCCGAGTGCTGGTAGACGGAGAAGAGCACGTCGGTT
TCCTTAAGACAGATGGGAGTTGTGGTCATGATATACTTCTGGATCTTATGTAGTGGAAAG
TTGTATCTCCAGCTTACAGATTGATCCCCTCGAGTGGATATCACTTCGAAAGGAAAATGA
GAGCAAGATATGTGAATTACATCAAAACATCAGAGGTTGTCAGACTGCCCTATCCTCTCCAAA
TGAAATCTCAGGTCCACCTTCTTACTTTATTAAAAGGAAATCGTGGGCTGGACAGACTTC
TAATGAACCCAATGGTTATGATGATGGTCTTCCTTATTGATATTGTGCTTCTGCCTAAAG
TGGTCAACACAAGTGATCCTGACATGAGACGGAAATGGAGCAGTCATGAATATGCTGAATT
CCAACCATGAGTTGCCTGATGTTCTGAGTTCATGACAAGACTCTCTTCCTCAAAATCATCTG
GCAAATCTAGCAGCGGCAGCAGTAAACAGGCAAAGTGGGCTGGCAAAGGAGGTAGTCAG
GCCGTCCAGAGCTGGCATTGCACAAACACGGCAACACTGGGTGGCATCCAAGTCTGGAAAAA
CCGTGTGAAGCAACTACTATAAAACTTGAGTCATCCGACGTTGATCTCTTACAACGTGTATGTT
AACTTTTAGCACATGTTGTACTGGTACACGAGAAAACCCAGCTTCATCTTGTCTGT
ATGAGGTCAATATTGATGTCACTGAATTAAATTACAGTGTCTATAGAAAATGCCATTAATAAA
TTATATGAACTACTATACATTATGTATATTAATTAAAACATCTTAATCCAGAAATCAAAAAAA
AAAAAAAAAAAAAAAAAAAAAA

136/168

FIGURE 136

MAAALWGFFPVLLLLLSDVQSSEVPGAAAEGSGSGVGIGDRFKIEGRAVPGVKPQDWIS
AARVLVDGEEHVGFLKTGDSFVVHDIPSGSYVVEVVSAYRFDPVVDITSKGKMRARYVNYI
KTSEVVRLPYPLQMKSSGPPSYFIKRESWGWTDFLMNPMVMMVLPLLIFVLLPKVVNTSDPD
MRREMEQSMNMLNSNHELPDVSEFMTRLFSSKSSGKSSGSSKTGKSGAGKRR

Important features of the protein:

Signal sequence:

amino acids 1-23

Transmembrane domain:

amino acids 161-182

N-glycosylation site.

amino acids 184-187

Glycosaminoglycan attachment sites.

amino acids 37-40, 236-239

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 151-154

N-myristoylation sites.

amino acids 33-38, 36-41, 38-44, 229-234

Amidation site.

amino acids 238-241

ATP/GTP-binding site motif A (P-loop).

amino acids 229-236

137/168

FIGURE 137

GATGGCGCAGCCACAGCTCTGTGAGATTGATTCAGTTCTCCCCAGTTCCCTGTGGGTCTGAGGG
GACCAGAAGGGTGAGCTACGTTGGCTTCTGGAAGGGGAGGCTATATGCGTCAATTCCCCAA
ACAAGTTTGACATTCCCTGAAATGTCATTCTATCTATTCACTGCAAGTGCCTGCTGTT
CCAGGCCTTACCTGCTGGCACTAACGGCGGAGCCAGGATGGGGACAGAATAAAGGAGCCACG
ACCTGTGCCACCAACTCGCACTCAGACTCTGAACACTCAGACCTGAAATCTTCTCTCACGGGAG
GCTTGGCAGTTTCTTACTCCTGTGGTCTCCAGATTCAAGGCCTAAGATGAAAGCCTCTAGT
CTTGCCTTCAGCCTCTCTGCTGCGTTTATCTCCTATGGACTCCTCACTGGACTGAAG
ACACTCAATTGGGAAGCTGTGTGATGCCACAAACCTTCAGGAAATACGAAATGGATTTCT
GAGATACGGGGCAGTGTGCAAGCCAAGATGAAACATTGACATCAGAATCTAAGGAGGACT
GAGTCTTGCAAGACACAAAGCCTGCGAATCGATGCTGCCTCCTGCGCCATTGCTAAGACTC
TATCTGGACAGGGTATTAAAAACTACCAGACCCCTGACCATTATACTCTCCGGAAAGATCAGC
AGCCTGCCAATTCTTCTTACCATCAAGAAGGACCTCCGGCTCTCATGCCACATGACA
TGCCATTGTGGGGAGGAAGCAATGAAGAAATACAGCCAGATTCTGAGTCACTTGAAAAGCTG
GAACCTCAGGCAGCAGTTGTGAAGGCTTGGGGAACTAGACATTCTCTGCAATGGATGGAG
GAGACAGAATAGGAGGAAAGTGTGCTGCTGCTAAGAATATTGAGGTCAAGAGCTCCAGTCT
TCAATACCTGCAGAGGAGGCATGACCCAAACCACCATCTCTTACTGTACTAGTCTGTGCT
GGTCACAGTGTATCTATTATGCATTACTGCTTCCTGCATGATTGTCTTATGCATCCCC
AATCTTAATTGAGACCATACTGTATAAGATTGGTAATATCTTCTGCTATTGGATATATT
TATTAGTTAATATATTATTATTGCTATTAATGTATTATTATTGACATG
AAACTTTAAAAAAATTCACAGATTATTTATAACCTGACTAGAGCAGGTGATGTATTGTAT
ACAGTAAAAAAAAACCTGTAAATTCTAGAAGAGTGGCTAGGGGGTTATTCAATTGTAT
TCAACTAAGGACATATTACTCATGCTGATGCTCTGTGAGATATTGAAATTGAACCAATGAC
TACTTAGGATGGGTTGTGGAATAAGTTGATGTGGAATTGCACATCTACCTACAATTACTG
ACCATCCCCAGTAGACTCCCCAGTCCATAATTGTGATCTTCCAGCCAGGAATCCTACACGG
CCAGCATGTATTCTACAAATAAGTTCTTGCATACCAAAAAAAAAAAAAAA

138/168

FIGURE 138

MRQFPKTSFDISPEMSFSIYSLQVPAVPG LTCWALTAEPGWGQNKGATT CATNSHSDSEL RPE
IFSSREAWQFFLLLWSPDFRPKMKASSLAFSLLSAAFYLLWTPSTGLKTLNLGSCVIATNLQE
IRNGFSEIRGSVQAKDGNIDIRILRRTESLQDTK PANRCCLLRHLLRLYLDRVFKNYQTPDHY
TLRKISSLANSFLT IKKDLRLSHAHMTCHCGEEAMKKYSQILSHFEKLEPQAAVVKALGELDI
LLQWMEETE

Important features of the protein:**Signal peptide:**

amino acids 1-42

cAMP- and cGMP-dependent protein kinase phosphorylation sites.

amino acids 192-195, 225-228

N-myristoylation sites.

amino acids 42-47, 46-51, 136-141

FIGURE 139

CCTGGAGCCGGAAAGCGCGGCTGCAGCAGGGCGAGGCTCCAGGTGGGTCGGTCCGCATCCAG
CCTAGCGTGTCCACG**ATG**CGGCTGGGCTCCGGGACTTCGCTACCTGTTGCGTAGCGATCGAG
GTGCTAGGGATCGCGGTCTCCTCGGGATTCTTCCCGCTCCGTTCTCGGCCAGA
GCAGAACACGGAGCGGGAGCCCCCAGCGCCCGAACCCCTCGGCTGGAGCCAGTTCTAAGTGGACC
ACGCTGCCACCACCTCTCTCAGTAAAGTTATTGTTCTGATAGATGCCTTGAGAGATGAT
TTTGTGTTGGGTCAAAGGGTGTGAAATTATGCCCTACACAACCTACCTTGTGGAAAAAGGA
GCATCTCACAGTTGTGGCTGAAGCAAAGCCACCTACAGTTACTATGCCCTGAATCAAGGCA
TTGATGACGGGGAGCCTCCTGGCTTGTGACGTCATCAGGAACCTCAATTCTCCTGCAC TG
CTGGAAGACAGTGTGATAAGACAAGCAAAGCAGCTGGAAAAAGAATAGTCTTTATGGAGAT
GAAACCTGGGTTAAATTATTCCCAAAGCATTGTGGAATATGATGGAACAAACCTCATTTC
GTGTCAGATTACACAGAGGTGGATAATAATGTCACGAGGCATTGGATAAAAGTATTAAAAGA
GGAGATTGGGACATATTAATCCTCACTACCTGGGCTGGACCACATTGCCACATTCAGGG
CCCAACAGCCCCCTGATTGGGAGAAGCTGAGCAGACAGCGTGTGATGAAGATCCAC
ACCTCACTGCACTGCAAGGAGAGAGAGACGCCATTACCAATTGCTGGTTCTTGTGGTGAC
CATGGCATGTCTGAAACAGGAAGTCACGGGCTCCTCCACCGAGGAGGTGAATACACCTCTG
ATTAAATCAGTTCTGCGTTGAAAGGAAACCCGGTGAATACCGACATCCAAAGCACGTCAA
TAGACGGATGTGGCTGCGACACTGGCGATAGCACTTGGCTTACCGATTCCAAAAGACAGTGTA
GGGAGCCTCCTATTCCAGTTGTGGAAGGAAGACCAATGAGAGAGCAGTTGAGATTTTACAT
TTGAATACAGTGCAGCTTAGTAAACTGTTGCAAGAGAATGTGCCGTATATGAAAAAGATCCT
GGGTTGAGCAGTTAAATGTCAGAAAGATTGCATGGGAACTGGATCAGACTGTACTTGGAG
GAAAGCATTCAAGTCCTATTCAACCTGGGCTCCAAGGTTCTCAGGCAGTACCTGGATGCT
CTGAAGACGCTGAGCTTGTCCCTGAGTGCACAAGTGGCCAGTTCTCACCCCTGCTCCTGCTCA
GCGTCCCACAGGCACTGCACAGAAAGCTGAGCTGGAAAGTCCCAGTGCATCTCCTGGTTTT
CTCTGCTTTTATTGGTGAACCTGGTGTGCAAGTGCAGGCTGGCAGTGCCTGGACAGGGGGCCTCAGG
CTGAAAGTTCGTGTACTTCTGTGGCCTCTCGTGGCTGGCGAGGCTGCCTTGTGAC
GAECTGGTTGAACACCTGGTGTGCAAGTGCAGGCTGGCAGTGCCTGGACACAGGTGTTACATCTGT
GCTGTCAGGTCAAGATGCCTCAGTTCTGGAAAGCTAGGTTCTGCGACTGTTACCAAGGTGAT
TGTAAAGAGCTGGCGGTACAGAGGAACAAGCCCCCAGCTGAGGGGGTGTGAATCGGACA
GCCTCCCAGCAGAGGTGTGGAGCTGCAGCTGAGGGAAAGAAGAGACAATCGGCCTGGACACTC
AGGAGGGTCAAAAGGAGACTTGGTCGACCAACTCATCTGCCACCCCCAGAATGCATCTGCC
TCATCAGGTCCAGATTCTTCCAAGGCAGCTTCTGTTGGAATTCTTAGTCCTGGCCT
CGGACACCTCATTGTTAGCTGGGAGTGGTGGTGAGGCAGTGAAGAAGAGGCGGATGGTCA
CACTCAGATCCACAGAGCCCAGGATCAAGGGACCCACTGCAGTGGCAGCAGGACTGTTGGCC
CCCACCCCAACCTGCACAGCCCTCATCCCCCTTGGCTTGAGCCGTCAAGGGCCCTGTGCTG
AGTGTCTGACCGAGACACTCACAGCTTGTGATCAGGGCACAGGCTTCTCGGAGCCAGGATG
ATCTGTGCCACGCTTGCACCTCGGGCCATCTGGGCTCATGCTCTCTCCTGCTATTGAATT
AGTACCTAGCTGCACACAGTATGTTACCAAAAGAATAACGGCAATAATTGAGAAAAAAA

140/168

FIGURE 140

MRLGSGTFATCCVAIEVLGIAVFLRGFFPAPVRSSARAEGAEPPAPEPSAGASSNWTLPPP
LFSKVIVILIDALRDDFVFGSKGVKFMPYTTYLVEKGASHSFVAEAKPPTVTMPRIKALMTGS
LPGFVDVIRNLNSPALLEDSVIRQAKAAGKRIVFYGDETWVKLFPKHFVEYDGTSFFVSDYT
EVDDNVTRHLDKVLKRGDWLILHYLGLDHIGHISGPNSPLIGQKLSEMDSVLMKIHTSLQS
KERETPLPNLLVLCGDHGMSETGSHGASSTEEVNTPLILISSAFERKPGDIRHPKHVQ

Important features of the protein:

Signal peptide:

amino acids 1-34

Transmembrane domain:

amino acids 58-76

N-glycosylation sites.

amino acids 56-60, 194-198

N-myristoylation sites.

amino acids 6-12, 52-58, 100-106, 125-131, 233-239, 270-276,
275-281, 278-284

Amidation site.

amino acids 154-158

Cell attachment sequence.

amino acids 205-208

141/168

FIGURE 141

GGCACGAGGCAAGCCTTCCAGGTTATCGTGACGCACCTGAAAGTCTGAGAGCTACTGCCCTA
CAGAAAGTTACTAGTGCCTAAAGCTGGCGCTGGCACTGATGTTACTGCTGCTGGAGTAC
AACTTCCCTATAGAAAACAACGCCAGCACCTTAAGACCACTCACACCTCAGAGTGAAGAAC
TTAAACCCGAAGAAATTAGCATTGACCAAGGATCACAAAGTACTGGTCCTGGACTCTGGG
AATCTCATAGCAGTCCAGATAAAAACATACGCCAGAGATCTTCTTGCAATTAGCCTCA
TCCTTGAGCTCAGCCTCTGGAGAAAGGAAGTCCGATTCTCCTGGGGTCTCTAAAGGGAG
TTTGCTCTACTGTGACAAGGATAAAGGACAAAGTCATCCATCCCTCAGCTGAAGAAGGAG
AAACTGATGAAGCTGGCTGCCAAAAGGAATCAGCACGCCGGCCTTCATCTTATAGGGCT
CAGGTGGCCTGGAACATGCTGGAGTCGGCGCTACCCCGGATGGTCATCTGCACCTCC
TGCAATTGTAATGAGCCTGTTGGGTGACAGATAAATTGAGAACAGGAAACACATTGAATT
TCATTCACCAGTTGCAAAGCTGAAATGAGCCCCAGTGAGGTCAAGCGATTAGGAACTGCC
CCATTGAACGCCTCCTCGCTAATTGAACTAATTGTATAAAACACCAAACCTGCTCACT

142/168

FIGURE 142

MLLLLLEYNFPPIENNQHLKTTHTFRVKNLNPKKFSIHQDHKVLVLDGNLIAVPDKNYIRP
EIFFALASSLSSASAEGSPILLGVSKGEFCLYCDKDKGQSHPSLQLKKEKLMKLAQKESAR
RPFIFYRAQVGWSWNMLESAAHPGWFICTSCNCNEPVGVTDKFENRKHIEFSFQPVCKAEMS
PS
EVSD

cAMP- and cGMP-dependent protein kinase phosphorylation site.
amino acids 33-36

N-myristoylation site.

amino acids 50-55, 87-92

Interleukin-1

amino acids 37-182

143/168

FIGURE 143

CTAGAGAGTATAGGGCAGAAGGATGGCAGATGAGTGACTCCACATCCAGAGCTGCCTCCCTT
AATCCAGGATCCTGTCCTCCTGTCCTGTAGGAGTGCCTGTTGCCAGTGTGGGTGAGACAAG
TTTGTCCCACAGGGCTGTCTGAGCAGATAAGATAAAGGGCTGGGTCTGTGCTCAATTAACTCC
TGTGGGCACGGGGCTGGAAAGAGCAAAGTCAGCGGTGCCTACAGTCAGCACCAATGCTGGGCC
TGCCGTGGAAGGGAGGTCTGTCCTGGCGCTGCTGCTGTTCTTAGGCTCCAGATCCTGC
TGATCTATGCCTGGCATTCCACGAGCAAAGGGACTGTGATGAACACAATGTCATGGCTCGTT
ACCTCCCTGCCACAGTGGAGTTGCTGTCCACACATTCAACCAACAGAGCAAGGACTACTATG
CCTACAGACTGGGGCACATCTTGAATTCTGGAAAGGAGCAGGTGGAGTCCAAGACTGTATTCT
CAATGGAGCTACTGCTGGGAGAACTAGGTGTGGAAATTGAAAGACGACATTGACAAC TGCC
ATTCCAAGAAAGCACAGAGCTGAACAATACTTCACCTGCTTCTCACCATCAGCACCAAGGC
CCTGGATGACTCAGTTCAGCCTCCTGAACAAGACCTGCTGGAGGGATTCCACTGAGTGAAAC
CCACTCACAGGCTTGTCCATGTGCTGCTCCCACATTCCGTGGACATCAGCACTACTCTCCTGA
GGACTCTTCAGTGGCTGAGCAGCTTGGACTTGTGTTATCCTATTTGCATGTGTTGAGA
TCTCAGATCAGTGTGTTAGAAAATCCACACATCTTGAGCCTAATCATGTAGTGTAGATCATTA
AACATCAGCATTAAAGAA
AAAAAAAAAAAAAAA

144/168

FIGURE 144

MLGLPWKGGLSWALLLLLLGSQILLIYAWHFHEQRDCDEHNVMARYLPATVEFAVHTFNQQSK
DYYAYRLGHILNSWKEQVESKTVFSMELLGRTRCGKFEDDIDNCHFQESTELNNTFTCFFT
STRPWMTQFSLLNKTCLEGFH

Important features of the protein:

Signal peptide:

amino acids 1-25

N-glycosylation sites.

amino acids 117-121, 139-143

N-myristoylation site.

amino acids 9-15

145/168

FIGURE 145

CTGTGCAGCTCGAGGCTCCAGAGGCACACTCCAGAGAGAGCCAAGGTTCTGACGCGATGAGGA
AGCACCTGAGCTGGTGGTGGCCACTGTCTGCATGCTGCTCTTCAGCCACCTCTGCGG
TCCAGACGAGGGGCATCAAGCACAGAACATCAAGTGGAACCGGAAGGCCCTGCCAGCACTGCC
AGATCACTGAGGCCAGGTGGCTGAGAACCGCCGGAGCCTCATCAAGCAAGGCCGCAAGC
TCGACATTGACTTCGGAGCCGAGGGCAACAGGTACTACGAGGCCAACTACTGGCAGTTCCCCG
ATGGCATCCACTACAACGGCTGCTCTGAGGCTAATGTGACCAAGGAGGCATTGTCACCGGCT
GCATCAATGCCACCCAGGCAGCGAACCAGGGGAGTTCCAGAACGCCAGACAACAAGCTCCACC
AGCAGGTGCTCTGGGGCTGGTCCAGGAGCTCTGCTCCCTCAAGCATTGCGAGTTGGTTGG
AGAGGGCGCAGGACTTCGGGTACCATGCACCCAGCCAGTGCTCCTCTGCCTCTGGCTTGA
TCTGGCTATGGTAAATAAGCTGCCAGGAGGCTGGCAGTACAGAGCGCAGCAGCAGCAAA
TCCTGGCAAGTGACCCAGCTCTTCTCCCCAAACCCACGCGTGTCTGAAGGTGCCAGGAGC
GGCGATGCACTCGCACTGCAAATGCCGCTCCACGTATGCCCTGGTATGTGCCCTGCGTTCT
GATAGATGGGGACTGTGGCTTCTCCGTACTCCATTCTCAGGCCCTAGCAGAGCGTCTGGCA
CACTAGATTAGTAGTAAATGCTTGATGAGAACACATCAGGCAGTGCGCCACCTGCTTCAC
AGTACTTCCAACAACACTTTAGAGGTAGGTGATTCCGTTTACAGATAAGGAAACTGAGGC
CCAGAGAGCTGAAGTACTGCACCCAGCATCACCAGCTAGAAAGTGGCAGAGGCCAGGATTCAAC
CCTGGCTTGTCTAACCCAGGTTCTGCTCTGCCAATTCCAGAGCTGTCTGGTGTACTT
TATGTCTCACAGGGACCCACATCCAAACATGTATCTCTAATGAAATTGTGAAAGCTCCATGTT
TAGAAATAATGAAAACACCTGA

146/168

FIGURE 146

MRKHLSWWWLATVCMLLFSHLSAVQTRGIKHRIKWNRKALPSTAQITEAQVAENRPGAFIKQG
RKLDIDFGAEGNRYYEANYWQFPDGIHYNGCSEANVTKEAFVTGCINATQAANQGEFQKPDNK
LHQQVLWRLVQELCSLKHFCEFWLERGAGLRVTMHQPVLLCLLALIWLVMVK

Important features of the protein:

Signal peptide:

amino acids 1-26

Transmembrane domain:

amino acids 157-171

N-glycosylation sites.

amino acids 98-102, 110-114

Tyrosine kinase phosphorylation site.

amino acids 76-83

N-myristoylation sites.

amino acids 71-77, 88-94, 93-99, 107-113, 154-160

Amidation site.

amino acids 62-66

147/168

FIGURE 147

GCCTTGGCCTCCAAAGGGCTGGATTATAGGCGTGACCACCATGTCTGGTCCAGAGTCTCAT
TTCCTGATGATTATAGACTCAAAGAAA**ACTC**ATGTTCAGAAGCTCTCTCTGGCCTC
CTCTCTGTCTTCTTCCCTCTTCTTATTAAATTAGTAGCATCTACTCAGAGTCATGCA
AGCTGGAAATCTTCATTTGCTTGTCACTGGGTAGGTACGTGAGTCTTAGTTTATTTTT
TGAAATTCAACTTCAGATTCAAGGGGTACATGTGAAGGTTGTTATGAGTATATTG**CAT**
GATGCTGAGGTTGGGT

148/168

FIGURE 148

MFRSSLLFWPPLCLLSLFLLILISSIYSESCKLEIFHFACQWGRSLSLSFYFLKFQLSDSGGT
CEGLFYEYIA

Important features of the protein:

Signal peptide:

amino acids 1-25

N-myristoylation site.

amino acids 62-68

FIGURE 149

GTCTCCGCGTCACAGGAACCTCAGCACCCACAGGGCGGACAGCGCTCCCTCTACCTGGAGAC
TTGACTCCCGCGGCCCAACCCCTGCTTATCCCTGACCGTCGAGTGTCAAGAGATCCTGCAGC
CGCCCAGTCCGGCCCTCTCCGCCACACCCACCCCTGGCTCTCCTGTTTACTCC
TCCTTTCAATTATAACAAAAGCTACAGCTCCAGGAGCCCAGCGCCGGCTGTGACCCAAGCC
GAGCGTGGAAAGAATGGGGTTCTCGGGACCGGCACTTGGATTCTGGTGTAGTGCTCCGATT
CAAGCTTCCCCAAACCTGGAGGAAGCCAAGACAAATCTACATAATAGAGAATTAAGTGCA
GAAAGACCTTGAAATGAACAGATTGCTGAAGCAGAAGACAAGATTAAAAAAACATATCCT
CCAGAAAACAAGCCAGGTAGAGCAACTATTCTTGATAACTTGAACCTGCTAAAGGCA
ATAACAGAAAAGGAAAAATTGAGAAAGAAAGACAATCTATAAGAAGCTCCCCACTTGATAAT
AAGTTGAATGTGGAAGATGTTGATTCAACCAAGAATCGAAAATGATCGATGATTATGACTCT
ACTAAGAGTGGATTGGATCATAAATTCAAGATGATCCAGATGGTCTTCATCAACTAGACGGG
ACTCCTTAACCGCTGAAGACATTGTCATAAAATCGCTGCCAGGATTATGAAGAAAATGAC
AGAGCCGTGTTGACAAGATTGTTCTAAACTACTTAATCTCGGCCTATCACAGAAAGCCAA
GCACATACACTGGAAGATGAAGTAGCAGAGGTTACAAAATTAATCTCAAAGGAAGCCAAC
AATTATGAGGAGGATCCAATAAGCCCACAAGCTGGACTGAGAATCAGGCTGGAAAAATACCA
GAGAAAGTGAATGCAATTGGCAGCAATTCAAGATGGTCTGCTAAGGGAGAAACGATGAAACA
GTATCTAACACATTAACCTTGACAAATGGCTGGAAAGGAGAACTAAAACCTACAGTGAAGAC
AACTTGAGGAACCTCAATATTCCAAATTCTATGCGCTACTGAAAAGTATTGATTGAGAA
AAAGAAGCAAAAGAGAAAGAAACACTGATTACTATCATGAAAACACTGATTGACTTGTGAAG
ATGATGGTGAATATGGAACAATATCTCCAGAAGAAGGTGTTCTACCTTGAAAACCTGGAT
GAAATGATTGCTCTCAGACCAAAACAAGCTAGAAAAAAATGCTACTGACAATATAAGCAAG
CTTTCCCAGCACCATTAGAGAAGAGTCATGAAGAACAGACAGTACCAAGGAAGAAGCAGCT
AAGATGGAAAAGGAATATGGAAGCTTGAGGATTCCACAAAGATGATAACTCCAACCCAGGA
GGAAAGACAGATGAACCCAAAGGAAAAACAGAAGCCTATTGGAAGCCATCAGAAAAATATT
GAATGGTTGAAGAAACATGACAAAAGGGAAATAAGAAGATTATGACCTTCAAAGATGAGA
GACTTCATCAATAACAAAGCTGATGCTTATGTGGAGAAAGGCATCCTGACAAGGAAGAAGCC
GAGGCCATCAAGCGCATTAGCAGCCTGTAAAAATGGCAAAAGATCCAGGAGTCTTCAAC
TGTTCAGAAAACATAATATAGCTAAAACACTTCTAATTCTGTGATTAAAATTGGACCC
AAGGGTTATTAGAAAGTGTGAATTACAGTAGTTAACCTTACAAGTGGTAAACATAGC
TTTCTCCCGTAAAACATCTGAAAGTAAAGTTGTATGTAAGCTGAAAAA
AAA

150/168

FIGURE 150

MGFLGTGTWILVLVLPIQAFPKPGGSQDKSLHNRELSAERPLNEQIAEAEEDKIKKTPPENK
PGQSNYSFVDNLNLKAITEKEKIEKERQSIRSSPLDNKLNVEDVDSTKNRKLIDDYDSTKSG
LDHKFQDDPDGLHQLDGTPLTAEDIVHKIAARIYEENDRAVFDKIVSKLLNLGLITESQAHTL
EDEVAEVLQKLISKEANNYEEDPNKPTSWTENQAGKIPEKVTPMAAIQDGLAKGENETVSNT
LTLTNGLERRTKTYSEDNFEELQYFPNFYALLKSIDSEKEAKEKETLITIMKTLIDFVKMMVK
YGTISPEEGVSYLENLDEMIALQTKNKNATDNISKLFPAPSEKSHEETDSTKEAAKMEK
EY GSLKDSTKDDNSNPGGKTDEPKGKTEAYLEAIRKNIEWLKKHDKGKGNKEDYDLSKMRDFIN
KQADAYVEKGILDKEEAEAIKRIYSSL

N-glycosylation sites:

amino acids 68-71, 346-349, 350-353

Casein kinase II phosphorylation site:

amino acids 70-73, 82-85, 97-100, 125-128, 147-150, 188-191, 217-
220, 265-268, 289-292, 305-308, 320-323, 326-329, 362-365, 368-
341, 369-372, 382-385, 386-389, 387-390

N-myristoylation sites:

amino acids 143-148, 239-244

FIGURE 151

CGGCTCGAGGGCTCCGCCAGGAGAAAGGAACATTCTGAGGGGAGTCTACACCCTGTGGAGCTC
AAGATGTCTGAGTGGGGCGCTGTGCTTCCGAATGAAGGACTCGGCATTGAAGGTGCTTTAT
CTGCATAATAACCAGCTCTAGCTGGAGGGCTGCATGCAGGGAAAGGTCACTAAAGGTGAAGAG
ATCAGCGTGGTCCCCAATCGGTGGCTGGATGCCAGCCTGTCCCCGTCACTCCTGGGTGTCCAG
GGTGGAAAGCCAGTGCCTGTCACTGTGGGTGGGGCAGGAGCCGACTCTAACACTAGAGCCAGTG
AACATCATGGAGCTCTATCTGGTCCAAGGAATCCAAGAGCTCACCTCTACCGGGCAGGAC
ATGGGGCTCACCTCCAGCTCGAGTCGGCTGCCTACCCGGCTGGTCTGTGCACGGTGCCT
GAAGCCGATCAGCCTGTCACTCACCCAGCTTCCCAGAATGGTGGCTGGAATGCCCATC
ACAGACTTCACTTCCAGCAGTGTGACT**TAGGG**CAACGTGCCCCCCAGAACTCCCTGGGCAGAG
CCAGCTCGGGTGAGGGTGAGTGGAGGAGACCCATGGCGGACAATCACTCTCTGCTCTCAG
GACCCCCACGTCTGACTTAGTGGCACCTGACCACTTGTCTTGTCTGGTCTCCAGTTGGATAA
ATTCTGAGATTGGAGCTCAGTCCACGGTCCTCCCCACTGGATGGTGCTACTGCTGTGGAAC
CTTGTAAAAACCATGTGGGGTAAACTGGGAATAACATGAAAAGATTCTGTGGGGGTGGGTG
GGGGAGTGGTGGGAATCATTCTGCTTAATGGTAACGTGACAAGTGTACCTGAGCCCCGAG
GCCAACCCATCCCCAGTTGAGCCTTATAGGGTCAGTAGCTCTCCACATGAAGTCTGTCACTC
ACCACTGTGCAGGAGAGGGAGGTGGTCATAGAGTCAGGGATCTATGGCCCTTGGCCAGCCCC
ACCCCCCTCCCTTAATCCTGCCACTGTCACTGCTACCTTTCTATCTCTCCCTCATCATC
TTGTTGTGGCATGAGGAGGTGGTGTGATGTCAGAAGAAATGGCTCGAGCTCAGAAGATAAAAGA
TAAGTAGGGTATGCTGATCCTCTTTAAAAACCCAAGATAACATCAAATCCCAGATGCTGGT
CTCTATTCCCATGAAAAAGTGTCACTGACATATTGAGAAGACCTACTTACAAAGTGGCATATA
TTGCAATTATTAAATTAAAAGATAACCTATTATATTATTTCTTATAGAAAAAGTCTGGAA
GAGTTTACTTCAATTGTAGCAATGTCAGGGTGGCAGTATAGGTGATTTCTTTAATTC
TGTTAATTATCTGTATTCTTAATTCTACAATGAAGATGAATTCTGTATAAAAATAA
GAAAAGAAAATTATCTGAGGTAAGCAGAGCAGACATCATCTGATTGTCCTCAGCCTCCAC
TTCCCCAGAGTAAATTCAAATTGAATGAGCTCTGCTGCTCTGGTTGGTTGTAGTAGTGTCA
GGAAACAGATCTCAGCAAAGCCACTGAGGAGGGCTGTGCTGAGTTGTGGCTGGAATCT
CTGGGTAAAGGAACCTAAAGAACAAAATCATGGTAATTCTTCTAGAAGGATCACAGCCC
CTGGGATTCCAAGGCATTGGATCCAGTCTAAGAAGGCTGCTGTACTGGTTGAATTGTGTCC
CCCTCAAATTACATCCTCTTGGAAATCTCAGTCTGTGAGTTATTGGAGATAAGGTCTCTG
CAGATGTAGTTAGTTAAGACAAGGTCACTGCTGGATGAAGGTAGACCTAAATTCAATATGACTG
GTTCTTGTATGAAAAGGAGAGGACACAGAGACAGAGGAGACGCGGGGAAGACTATGTAAAG
ATGAAGGCAGAGATCGGAGTTTGCAAGCCACAAGCTAACAGAAACACCAAGGATTGTGGCAACCA
TCAGAAGCTTGGAGAGGCAAAGAAGAATTCTCCCTAGAGGCTTATAGAGGATAACGGCTCT
GCTGAAACCTTAATCTCAGACTTCCAGCCTCTGAACGAAGAAGAATAAAATTGGCTGTT
TAAGCCACCAAGGATAATTGGTTACAGCAGCTCTAGGAAACTAACAGCTGCTAAATGATC
CCTGTCTCCTCGTGTGTTACATTCTGTGTGTCCTCCACAAATGTACCAAGTTGTCTTG
TGACCAATAGAATATGGCAGAAGTGTGATGGCATGCCACTTCAAGATTAGGTTATAAAAGACAC
TGCAGCTTCACTTGAGCCCTCTCTGCCCCACCGCCCCAATCTATCTGGCTCACT
CGCTCTGGGGGAAGCTAGCTGCCATGCTATGAGCAGGCTATAAAGAGACTTACGTGGTAAA
AATGAAGTCTCCTGCCACAGCCACATTAGTGAACCTAGAACGAGAGACTCTGTGAGATAATC
GATGTTGTGTTAAGTTGCTCAGTTGGTCTAACCTGTTATGCAGCAATAGATAAAATAA
TATGCAGAGAAAGAG

152/168

FIGURE 152

MVLSGALCFRMKDSALKVLYLHNNQLLAGGLHAGKVIKGEEISVVPNRWLDASLSPVILGVQG
GSQCLSCGVGQEPTLTLEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWFLCTVPE
ADQPVRLTQLPENGGWNAPITDFYFQQCD

N-myristylation sites.

amino acids 29-34, 30-35, 60-65, 63-68, 73-78, 91-96, 106-111

Interleukin-1 signature.

amino acids 111-131

Interleukin-1 proteins.

amino acids 8-29, 83-120, 95-134, 64-103

FIGURE 153

CTTCAGAACAGGTTCTCCTCCCCAGTCACCAGTTGCTCGAGTTAGAATTGTCTGCAATGGCC
GCCCTGCAGAAATCTGTGAGCTTTCCCTATGGGGACCCTGCCACCAGCTGCCCTCCTCTC
TTGGCCCTCTGGTACAGGGAGGAGCAGCTGCGCCCATCAGCTCCACTGCAGGCTTGACAAG
TCCAACCTCCAGCAGCCCTATATCACCAACCGCACCTCATGCTGGCTAAGGAGGCTAGCTTG
GCTGATAACAACACAGACGTTCGTCTCATTGGGGAGAAACTGTTCCACGGAGTCAGTATGAGT
GAGCGCTGCTATCTGATGAAGCAGGTGCTGAACCTCACCCCTGAAGAAGTGCTGTTCCCTCAA
TCTGATAGGTTCCAGCCTTATATGCAGGAGGTGGTGCCCTCCTGCCAGGCTCAGAACAGG
CTAACGCACATGTCATATTGAAGGTGATGACCTGCATATCCAGAGGAATGTGCAAAAGCTGAAG
GACACAGTAAAAAGCTGGAGAGAGTGGAGAGATCAAAGCAATTGGAGAACTGGATTGCTG
TTTATGTCTCTGAGAAATGCCTGCATTTGACCAGAGCAAAGCTGAAAAATGAATAACTAACCC
CCTTCCCTGCTAGAAATAACAATTAGATGCCCAAAGCGATTTTTAACAAAAGGAAGA
TGGGAAGCCAAACTCCATCATGATGGGTGGATTCCAAATGAACCCCTGCGTTAGTTACAAAGG
AAACCAATGCCACTTTGTTATAAGACCAGAAGGTAGACTTCTAACGCATAGATATTATTG
ATAACATTTCATTGTAACTGGTGTCTATACACAGAAAACAATTATTAAATAATTGTC
TTTTCCATAAAAAAGATTACTTCCATTCTTAGGGAAAAACCCCTAAATAGCTTCATG
TTCCATAATCAGTACTTTATTTATAAATGTATTATTATTATAAGACTGCATT
TTATATCATTAAATATGGATTATTAGAAACATCATTGATATTGCTACTTGAGTG
TAAGGCTAATATTGATATTATGACAATAATTAGAGCTATAACATGTTATTGACCTCAA
TAAACACTGGATATCCC

154/168

FIGURE 154

MAALQKSVSSFLMGTLATSCLLLALLVQGGAAAPISSHCRLDKSNFQQPYITNRTFMLAKEA
SLADNNTDVRLIGEKLFHGVSMSERCYLMQVLNFTLEEVLFQSDRFQPYMQUEVVPFLARLS
NRLSTCHIEGDDLHIQRNVQKLKDTVKKLGESGEIKAIGELDLLFMSLRNACI

Important features of the protein:

Signal peptide:

amino acids 1-33

N-glycosylation sites.

amino acids 54-58, 68-72, 97-101

N-myristylation sites.

amino acids 14-20, 82-88

Prokaryotic membrane lipoprotein lipid attachment site.

amino acids 10-21

FIGURE 155

GGCTTGCTGAAAATAAAATCAGGACTCCTAACCTGCTCCAGTCAGCCTGCTTCCACGAGGCCT
GTCAGTCAGTCCCCGACTTGTGACTGAGTGTGCAGTGCCAGCATGTACCAGGTCA
GGGCTGCCTGAGGGCTGTGCTGAGAGGGAGAGGAGCAGAGATGCTGCTGAGGGTGGAGGGAGG
CCAAGCTGCCAGGTTGGGCTGGGGCCAAGTGGAGTGAGAAACTGGGATCCCAGGGGAGG
GTGCAG**TG**AGGGAGCGACCCAGATTAGGTGAGGACAGTTCTCATTAGCCTTCTACAG
GTGGTTGCATTCTTGGCAATGGTCATGGGAACCCACACCTACAGCCACTGGCCAGCTGCTGC
CCCAGCAAAGGGCAGGACACCTCTGAGGAGCTGCTGAGGTGGAGCACTGTGCCTGTGCCTCCC
CTAGAGCCTGCTAGGCCAACCGCCACCCAGAGTCCTGTAGGGCCAGTGAAGATGGACCCCTC
AACAGCAGGGCCATCTCCCCCTGGAGATATGAGTTGGACAGAGACTTGAACCGGCTCCCCAG
GACCTGTACCACGCCGTTGCCGTGCCCGCACTGCGTCAGCCTACAGACAGGCTCCCACATG
GACCCCCGGGGCAACTCGGAGCTGCTTACACACAACCAGACTGTCTTACAGGCGGCCATGC
CATGGCGAGAAGGGACCCACAAGGGCTACTGCCCTGGAGCGCAGGCTGTACCGTGTTCCTTA
GCTTGTGTGTGTGCCGCCCCGTGTGATGGGCT**AG**CCGGACCTGCTGGAGGCTGGTCCCTT
TTGGGAAACCTGGAGCCAGGTGTACAACCACTTGCATGAAGGGCCAGGATGCCAGATGCTT
GGCCCTGTGAAGTGTGTGGAGCAGCAGGATCCGGGACAGGATGGGGGCTTGGGAA
AACCTGCACTTCTGCACATTTGAAAAGAGCAGCTGCTGCTTAGGGCCGGAAAGCTGGTGT
CCTGTCATTTCTCTCAGGAAAGGTTCAAAGTTCTGCCATTCTGGAGGCCACCACTCCT
GTCTCTCCTCTTCCATCCCTGCTACCCCTGGCCAGCACAGGCACCTTAGATATTTC
CCCCCTGCTGGAGAAGAAAGAGCCCTGGTTTATTGTTACTCATCACTCAGTGAGC
ATCTACTTTGGGTGCATTCTAGTGTAGTTACTAGTCTTGTACATGGATGATTCTGAGGAGGA
AGCTGTTATTGAATGTATAGAGATTATCCAAATAATCTTATTAAAAATGAAAAAA

156/168

FIGURE 156

MRERPRLGEDSSLISLFLQVVAFLAMVMGHTYSHWPSCCPKGQDTSEELLRWSTVPVPPLE
PARPNRHPESCRASEDGPLNSRAISPWRYELDRDLNRLPQDLYHARCLCPHCVSLQTGSHMDP
RGNSELLYHNQTVFYRRPCHGEKGTHKGYCLERRLYRVSLACVCVRPRVMG

Important features of the protein:

Signal peptide:

amino acids 1-32

N-glycosylation site.

amino acids 136-140

Tyrosine kinase phosphorylation site.

amino acids 127-135

N-myristoylation sites.

amino acids 44-50, 150-156

FIGURE 157

CCGGCGATGTCGCTCGTGTGCTAACGCTGGCCGCGCTGTGCAGGAGCGCCGTACCCCGAGAG
CCGACCGTTCAATGTGGCTCTGAAACTGGGCCATCTCCAGAGTGGATGCTACAAACATGATCTA
ATCCCCGGAGACTTGAGGGACCTCCGAGTAGAACCTGTTACAACTAGTGTGCAACAGGGGAC
TATTCAATTGATGAATGTAAGCTGGGTACTCCGGCAGATGCCAGCATCCGCTTGTGAAG
GCCACCAAGATTGTGTGACGGGCAAAAGCAACTTCCAGTCCTACAGCTGTGAGGTGCAAT
TACACAGAGGCCTTCCAGACTCAGACCAGACCCCTCTGGTGGTAAATGGACATTTCTACATC
GGCTTCCCTGTAGAGCTGAACACAGTCTATTTCATTGGGCCATAATATTCTAATGCAAAT
ATGAATGAAGATGGCCCTTCCATGTGTGAATTTCACCTCACAGGCTGCCTAGACCACATA
ATGAAATATAAAAAAAAGTGTGTCAAGGCCAGAACGCTGTGGATCCGAACATCACTGCTTGT
AAGAAGAATGAGGAGACAGTAGAAGTGAACCTCACACCACCTCCCTGGAAACAGATACTG
GCTCTTATCCAACACAGCACTATCATGGGTTTCTCAGGTGTTGAGCCACACCAGAAGAAA
CAAACGCGAGCTCAGTGGTATTCCAGTGACTGGGATAGTGAAGGTGCTACGGTGCAGCTG
ACTCCATATTTCTACTTGTGGCAGCGACTGCATCCGACATAAGGAACAGTTGTGCTCTGC
CCACAAACAGGCCTTCCCTCTGGATAACAACAAAAGCAAGCCGGAGGCTGGCTGCCT
CTCCTCCTGCTGTCTGCTGGTGGCCACATGGTGCTGGCAGGGATCTATCTAATGTGG
AGGCACGAAAGGATCAAGAAGACTTCCTTTCTACCACCAACTACTGCCCCCCATTAAGGTT
CTTGTGGTTACCCATCTGAAATATGTTCCATCACACAATTGTTACTCACTGAATTCTT
CAAAACCATTGCAGAAGTGAGGTATCCTGAAAAGTGGCAGAAAAAGAAAATAGCAGAGATG
GGTCCAGTGCAGTGGCTGCCACTCAAAAGAAGGCAGCAGACAAAGTCGTCTCCTCTTCC
AATGACGTCAACAGTGTGTGCGATGGTACCTGTGGCAAGAGCGAGGGCAGTCCAGTGAGAAC
TCTCAAGACCTTTCCCCCTGCCTTAACCTTTCTGCAGTGATCTAAGAAGCCAGATTCT
CTGCACAAATACGTGGTGGTCACTTAGAGAGATTGATAACAAAGACGATTACAATGCTCTC
AGTGTCTGCCCAAGTACCACTCATGAAGGATGCCACTGCTTCTGTGCAGAACTCTCCAT
GTCAAGCAGCAGGTGTCAGCAGGAAAAAGATCACAGCCTGCCACGATGGCTGCTCCTTG
TAG

FIGURE 158

MSLVLLSLAALCRSAVPREPTVQCGSETGPSPEWMLQHDLIPGDLRDLRVEPVTSVATGDYS
ILMNVSWVLRADASIRLLKATKICVTGKSNFQSYSCVRCNYTEAFQTQTRPSGGKWTFSYIGF
PVELNTVYFIGAHNIPNANMNEGPGSMSVNFTSPGCLDHIMKYKKKCVKAGSLWDPNITACKK
NEETVEVNFTTTPLGNRYMALIQHSTIIGFSQVFEPHQKKQTRASVVIPTGDSEGATVQLTP
YFPTCGSDCIRHKGTVVLCPQTGVFPLDNNKSKPGWLPLLLLSLLVATWVLVAGIYLMWRH
ERIKKTSFSTTLLPPIKVLVVYPSEICFHHTICYFTEFLQNHCRSEVILEKWQKKKIAEMGP
VQWLATQKKAADKVVFLSNDVNSVCDGTCGKSEGSPSENSQDLFPLAFNLFCSDLRSQIHLH
KYVVVYFREIDTKDDYNALSVCPKYHLMKDATAFCAELLHVKQQVSAGKRSQACHDGCCSL

Important features of the protein:

Signal peptide:

amino acids 1-14

Transmembrane domain:

amino acids 290-309

N-glycosylation sites.

amino acids 67 - 71, 103 - 107, 156 - 160, 183 - 187, 197 - 201
and 283 - 287

cAMP- and cGMP-dependent protein kinase phosphorylation sites.

amino acids 228 - 232 and 319 - 323

Casein kinase II phosphorylation sites.

amino acids 178 - 182, 402 - 406, 414 - 418 and 453 - 457

N-myristoylation site.

amino acids 116-122

Amidation site.

amino acids 488-452

FIGURE 159

AGCCACCAGCGAACATGACAGTGAAGACCCCTGCATGCCAGCCATGGTCAAGTACTTGCTG
CTGTCGATATTGGGGCTTGCCCTTCTGAGTGAGGCAGCTCGGAAAATCCCCAAAGTAGGA
CATACTTTTCCAAAAGCCTGAGAGTTGCCGCCTGTGCCAGGAGGTAGTATGAAGCTTGAC
ATTGGCATCATCAATGAAAACCAGCGCGTTCCATGTCACGTAACATCGAGAGGCCGCTCCACC
TCCCCCTGGAATTACACTGTCACTTGGGACCCCAACCGGTACCCCTCGGAAGTTGTACAGGCC
CAGTGTAGGAACTTGGGCTGCATCAATGCTCAAGGAAAGGAAGACATCTCCATGAATTCCGTT
CCCATCCAGCAAGAGACCCCTGGTCGTCCGGAGGAAGCACCAAGGCTGCTCTGTTCTTCCAG
TTGGAGAAGGTGCTGGTGAUTGTTGGCTGCACCTGCGTCACCCCTGTCATCCACCATGTGCAG
TAAGAGGTGCATATCCACTCAGCTGAAGAAG

160/168

FIGURE 160

MTVKTLHGPAMVKYLLSILGLAFLSEAAARKIPKGHTFFQKPESCPPVPGGSMKLDIGIIN
ENQRVMSRNIESRSTSPWNYTVTWDPNRYPSEVVQAQCRNLGCINAQGKEDISMNSVPIQQE
TLVVRRKHQGCSVSFQLEKVLVTVGCTCVTPVIIHHVQ

Signal sequence:

amino acids 1-30

N-glycosylation site.

amino acids 83-87

N-myristoylation sites.

amino acids 106-111, 136-141

FIGURE 161

ACACTGGCAAACAAAAACGAAAGCCTCCGTGCTGGAAGTAGGAGGAGAGTCAGGACTCCCA
GGACAGAGAGTGCACAAACTACCCAGCACAGCCCCCTCCGCCCCCTGGAGGCTGAAGAGGG
ATTCCAGCCCCCTGCCACCCACAGACACAGGGCTGACTGGGTGTCCTGCCCCCTGGGGGGGG
CAGCACAGGGCCTCAGGCCTGGTGCACCTGGCACCTAGAAGATGCCTGTGCCCTGGTTCTT
GCTGTCCTGGCACTGGCGAAGGCCAGTGGCTTCTCTGGAGAGGGCTTGTGGGCCTCA
GGACGCTACCCACTGCTCTCCGGCCTCTCGCCGCCTCTGGGACAGTGACATACTCTGCCT
GCCTGGGACATCGCTGCTCCGGCCCCGTGCTGGCGCTACGCACCTGCAGACAGAGCT
GGTGTGAGGTGCCAGAAGGAGACCGACTGTGACCTCTGTCTGCGTGTGGCTGTCCACTGGC
CGTGCATGGGCACTGGGAAGAGCCTGAAGATGAGGAAAAGTTGGAGGAGCAGCTGACTCAGG
GGTGGAGGAGCCTAGGAATGCCCTCTCCAGGCCAAGTCGTGCTCTCCAGGCCTACCC
TACTGCCCGCTGCGTCTGCTGGAGGTGCAAGTGCCTGCTGCCCTGTGCAGTTGGTCAGTC
TGTGGCTCTGTGGTATATGACTGCTCGAGGCTGCCCTAGGGAGTGAGGTACGAATCTGGTC
CTATACTCAGCCCAGGTACGAGAAGGAACCTAACACACAGCAGCTGCCCTGCCCTG
GCTAACGTGTCAGCAGATGGTACAACGTGCATCTGGTCTGAATGTCCTGAGGAGCAGCA
CTTCGGCCTCTCCCTGTAUTGGAAATCAGGTCCAGGGCCCCAAAACCCCGTGGCACAAAAA
CTGACTGGACCGCAGATCATTACCTGAACACACAGACCTGGTCCCTGCCCTGTATTCA
GGTGTGGCCTCTGGAACCTGACTCCGTTAGGACGAACATCTGCCCTTCAGGGAGGACCCCG
CGCACACCAGAACCTCTGGCAAGCCGCCGACTGCGACTGCTGACCCCTGCAGAGCTGGCTGCT
GGACGCACCGTGCTCGCTGCCGCAGAAGCAGCACTGTGCTGGCAGGCTCCGGTGGGACCC
CTGCCAGCCACTGGTCCCACCGCTTCTGGAGAACGTCACTGTGGACAAGGTTCTGAGTT
CCCATTGCTGAAAGGCCACCTAACCTCTGTGTTCAAGGTGAACAGCTCGGAGAAGCTGCAGCT
GCAGGAGTGTGTTGGCTGACTCCCTGGGGCTCTCAAAGACGATGTGCTACTGTTGGAGAC
ACGAGGCCCCCAGGACAACAGATCCCTCTGTGCTGGCTGGAAACCCAGTGGCTGACTTCAC
CAGCAAAGCCTCCACGAGGGCAGCTGCCCTGGAGAGTACTTACTACAAGACCTGCAGTCAGG
CCAGTGTCTGCAGCTATGGGACGATGACTTGGGAGCGCTATGGCCTGCCCATGGACAAATA
CATCCACAAGCGCTGGGCCCTCGTGTGGCTGCCCTACTCTTGCCGCTGCCTTCCCT
CATCCCTCTCTCAAAAGGATCACGCGAAAGGGTGGCTGAGGCTCTTGAAACAGGACGTCCG
CTCGGGGGCGGCCAGGGGCCGCGCGCTCTGCTCCTACTCAGCCGATGACTGGGTT
CGAGCGCCTGGTGGCGCCCTGGCGTCGGCCCTGTGCCAGCTGCCGCTGCGCTGGCGTAGA
CCTGTTGGAGGCCGTCGTGAACGTGAGCGCGCAGGGGCCGTGGCTGGTTACGCGCAGCG
CCAGACCCCTGCAGGAGGGCGCGTGGTGGCTTGCTCTCTCCGGTGCAGGCTGGCGTAG
CAGCGAGTGGCTACAGGATGGGTGTCGGCCGACTTCTGCAAGGGCCGGCGCCGGCAGCTAC
CGCCTCGCTCAGCTGCGTGCCTGCCGACTTCTGCAAGGGCCGGCGCCGGCAGCTAC
GGCCTGCTTCGACAGGCTGCTCCACCCGGACGCCGTACCCGCCCTTTCCGCACCGTGC
CTTCACACTGCCCTCCAACTGCCAGACTTCTGGGGCCCTGCAGCAGCCTCGCGCCCCCG
TTCCGGCGGCTCCAAGAGAGAGCGGGAGCAAGTGTCCGGCCCTTCAGCCAGCCCTGG
CTAATTCCATCCCCGGGACTCCCGCGCAGGGACGCCGGTGGACCAGGGCGGGACCTGG
GGCGGGGGACGGGACTTAAATAAGGCAGACGCTGTTTTCTAAAAAAA

FIGURE 162

MPVPWFLLSLALGRSPVVLSLERLVGPQDATHCSPGLSCLRWDSDILCLPGDIVPAPGPVLAP
THLQTELVLRCQKETDCDLCLRVAVHLAVGHWEEPEDEEKFGGAADSGVEEPRNASLQAQVV
LSFQAYPTARCVLLEVQVPAALVQFGQSVGSVYDCFEAALGSEVRIWSYTQPRYEKELNHTQ
QLPALPWLNVSADGDNVHLVNVSEEQHFGLSLYWNQVQGPPKPRWHKNLTGPQIITLNHTDL
VPCLCIQVWPLEPDSVRTNICPFREDPRAHQNLWQAARLRLTLQSWLLDAPCSLPAEAALCW
RAPGGDPCQPLVPPPLSWENVTVDKLEFPPLKGHPNLCVQNSSEKQLQECIWADSLGPLKD
DVLLLETRGPCQDNRSLCALEPSGCTSLPSKASTRAARLGEYLLQDLQSGQCLQLWDDDLGALW
ACPMDKYIHKRWALVWLACLLFAAALSLILLKKDHAKGWLRLKQDVRSGAAARGRAALLLY
SADDSGFERLVGALASALCQLPLRVAVDLWSRRELSAQGPVAWFHAQRRQTLQEGGVVVLLFS
PGAVALCSEWLQDGVSGPGAHGPHDAFRASLSCVLPDFLQGRAPGSYVGACFDRLLHPDAVPA
LFRTVPVFTLPSQLPDFLGALQQPRAPRSGRLQERAEQVSRALQPALDSYFHPPGT PAPGRGV
GPGAGPGAGDGT

Signal sequence:

amino acids 1-20

Transmembrane domain.

amino acids 453-475

N-glycosylation sites.

amino acids 118-121, 186-189, 198-201, 211-214, 238-241, 248-251,
334-337, 357-360, 391-394

Glycosaminoglycan attachment site.

amino acids 583-586

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 552-555

N-myristylation sites.

amino acids 107-112, 152-157, 319-324, 438-443, 516-521, 612-617,
692-697, 696-701, 700-705

FIGURE 163

GGGAGGGCTCTGTGCCAGCCCCGATGAGGACGCTGCTGACCATCTGACTGTGGGATCCCTGG
CTGCTCACGCCCTGAGGACCCCTCGGATCTGCTCCAGCACGTGAAATTCCAGTCCAGCAACT
TTGAAAACATCCTGACGTGGACAGCGGGCCAGAGGGCAGCCAGACACGGTCTACAGCATCG
AGTATAAGACGTACGGAGAGAGGGACTGGGTGGCAAAGAAGGGCTGTCAGCGGATCACCGGA
AGTCCTGCAACCTGACGGTGGAGACGGCAACCTCACGGAGCTACTATGCCAGGGTACCCGCT
GTCAGTGCAGGGAGGCCGGTACGCCACCAAGATGACTGACAGGTTCAGCTCTGCAGCACACT
ACCCTCAAGCCACCTGATGTGACCTGTATCTCAAAGTGAGATCGATTAGATGATTGTCAT
CCTACCCCCACGCCAATCCGTGCAGCGATGCCACCGCTAACCTGGAAGACATCTCCAT
GACCTGTTCTACCACTTAGAGCTCCAGGTCAACCGCACCTACCAAATGCACCTGGAGGGAAG
CAGAGAGAATATGAGTTCTCGGCCCTGACCCCTGACACAGAGTTCTGGCACCATCATGATT
TGCCTCCCACCTGGCCAAGGAGAGTGCCCCCTACATGTGCCAGTGAAAGACACTGCCAGAC
CGGACATGGACCTACTCCTCTCCGGAGCCTCTGTTCTCATGGGCTCTCGTCGAGTA
CTCTGCTACCTGAGCTACAGATATGTCACCAAGCCGCTGCACCTCCAACTCCCTGAACGTC
CAGCGAGTCTGACTTCCAGCCGCTGCGCTTCATCCAGGAGCACGTCTGATCCCTGTCTT
GACCTCAGCGGCCAGCAGTCTGGCCAGCCTGTCCAGTACTCCAGATCAGGGTGTCTGGA
CCCAGGGAGCCCGCAGGAGCTCACAGCGGCATAGCCTGTCCAGATCACCTACTTAGGGCAG
CCAGACATCTCCATCCTCCAGCCCTCCAACGTGCCACCTCCCCAGATCCTCTCCCCACTGTCC
TATGCCCTAACGCTGCCCTGAGGTGGGGCCCCATCCTATGCACCTCAGGTGACCCCCGAA
GCTCAATTCCCATTCTACGCCAACAGGCCATCTAAGGTCCAGCCTCTCTATGCCCT
CAAGCCACTCCGGACAGCTGCCCTCCTATGGGTATGCATGGAAGGTTCTGGCAAAGAC
TCCCCCACTGGGACACTTCTAGTCTAAACACCTTAGGCCTAAAGGTCAAGCTCAGAAAGAG
CCACCACTGGAAGCTGCATGTTAGGTGGCCTTCTCTGCAGGAGGTGACCTCCTGGCTATG
GAGGAATCCAAGAAGCAAATCATTCAGCACCAGCCCTGGGGATTGACAGACAGAACATCT
GACCCAAATGTGCTACACAGTGGGAGGAAGGGACACCACAGTACCTAAAGGGCAGCTCCC
CTCCTCTCCTCAGTCCAGATCGAGGCCACCCATGCCCCCTTGTCAACCTCCTCCGGT
CCATGTTCCCCCTCGGACCAAGGTCCAAGTCCCTGGGGCTGCTGGAGTCCCTGTGTGCCCC
AAGGATGAAGCCAAGAGGCCAGCCCTGAGACCTCAGACCTGGAGCAGCCCACAGAACCTGGAT
TCTCTTTCAGAGGCCTGGCCCTGACTGTGCAGTGGGAGTCCTGAGGGAATGGAAAGGCTT
GGTCTTCCCTCCCTGTCCTACCCAGTGTACATCCTGGCTGTCATCCCAGTGCCTGCCAT
GCCACACACTCTGCGATCTGGCCTCAGACGGGTGCCCTTGAGAGAAGCAGAGGGAGTGGCATG
CAGGGCCCTGCCATGGGTGCGCTCTCACCGGAACAAAGCAGCATGATAAGGACTGCAGCGG
GGGAGCTGGGGAGCAGCTGTGAGACAAGCGCGTGCCTGAGCCCTGCAAGGCAGAAA
TGACAGTGAAGGAGGAATGCAGGGAAACTCCCAGGGTCCAGAGCCCCACCTCTAACACCA
TGGATTCAAAGTGCCTAGGGAAATTGCTCTCCTGGCCATTCTGGCCAGTTCACAAATCT
AGCTCGACAGAGCATGAGGCCCTGCCCTTCTGTCTTGTCAAGGTGGGAAGAGAGCCTG
GAAAAGAACCAAGGCCCTGGAAAAGAACCAAGAACAGAAGGAGGCTGGCAGAACCAACCTGC
TCTGCCAAGGCCAGGGCAGCAGGACGGCAGGACTCTAGGGAGGGTGTGGCCTGAGCTCAT
TCCAGCCAGGGCAACTGCCCTGACGTTGCACGATTCAGCTTCAATTCTCTGATAGAACAAAG
CGAAATGCAGGTCCACCAGGGAGGGAGACACACAAGCCTTCTGCAGGCAGGAGTTCAGAC
CCTATCCTGAGAATGGGGTTGAAAGGAAGGTGAGGGCTGTGGCCCTGGACGGTACAATAA
CACACTGTACTGATGTCACAACCTTGCAAGCTCTGCCCTGGGTCAGCCCATCTGGCTCAAA
TTCCAGCCTCACCACTCACAAGCTGTGACTCAAACAAATGAAATCAGTGCCAGAACCTC
GGTTCCCTCATCTGTAATGTGGGGATCATAACACCTACCTCATGGAGTTGTGGTGAAGATGAA
ATGAAGTCATGTCTTAAAGTGTAAATAGTGCCTGGTACATGGCAGTGCCAATAAACGGT
AGCTATTTAAAAAAAAAAAAAA

164/168

FIGURE 164

MRTLLTILTVGSLAAHAPEDPSDLLQHVKFQSSNFENILTWDSGPEGTPDTVYSIEYKTYGER
DWVAKKGQRITRKSCNLTVETGNLTELYYARVTAVSAGGRSATKMTDRFSSLQHTTLKPPDV
TCISKVRSIQMIVHPTPTPIRAGDGHRLTLEDIFHDLFYHLELQVNRTYQMHLGGKQREYEFF
GLTPDTEFLGTIMICVPTWAKESAPYMCRVKTLPDRTWTYSFSGAFLFSMGFLVAVLCYLSYR
YVTKPPAPPNSLNQRVLTQPLRFIQEHVLIPVFDLSGPSSLAQPVQYSQIRVSGPREPAGA
PQRHSLSEITYLGQPDISILQPSNVPPPQILSPLSYAPNAAPEVGPPSYAPQVTPEAQFPFYA
PQAIISKVQPSYYAPQATPDSWPPSYGVCMEGSGKDSPTGTLSSPKHLRPKGQLQKEPPAGSCM
LGGLSLQEVTSAMEESQEAQLHQPLGICTDRTSDPNVLHSGEEGTPQYLGQLPLLSSVQI
EGHPMSLPLQPPSGPCSPSDQGPSPWGLLESVCPKDEAKSPAPETSDLEQPTELDSLFRGLA
LTVQWES

Signal sequence.

amino acids 1-17

Transmembrane domain.

amino acids 233-250

N-glycosylation sites.

amino acids 80-83, 87-90, 172-175

N-myristoylation sites.

amino acids 11-16, 47-52, 102-107, 531-536, 565-570

165/168

FIGURE 165

TGGCCTACTGGAAAAAAAAAAAAAAAGTCACCCGGGCCGCCGGTGGCCACAACAT
GGCTGCGGCCGGGCTGCTCTTCTGGCTGTCGTGGGGCGCTCTGGTGGGTCCGGG
CCAGTCGGATCTCAGCCACGGACGGCGTTCTGGACCTCAAAGTGTGCAGGGACGAAGAGTG
CAGCATGTTAATGTACCGTGGAAAGCTCTTGAAGACTTCACGGCCCTGATTGTCGTTGT
GAATTTAAAAAAGGTGACGATGTATATGTCTACTACAAACTGGCAGGGGATCCCTGAACT
TTGGGCTGGAAGTGTGAACACAGTTGGATATTTCCAAAGATTGATCAAGGTACTTCA
TAAATACACGGAAGAAGAGCTACATATTCCAGCAGATGAGACAGACTTGTCTGCTTGAAGG
AGGAAGAGATGATTTAATAGTTATAATGTAGAAGAGCTTTAGGATCTTGGAACTGGAGGA
CTCTGTACCTGAAGAGTCGAAGAAAGCTGAAGAAGTTCTCAGCACAGAGAGAAATCTCCTGA
GGAGTCTCGGGGGCGTGAACTTGACCTGTGCCTGAGCCGAGGCATTAGCTGAGCTGATTAGA
GGATGGAGAAGGTGCTTCTCAGAGAGCACCGAGGGCTGCAGGGACAGCCCTAGCTCAGGA
GAGCCACCCCTCACACCAGCGGTCTGGCTAACGCTCAGGGAGTCAGTCTCGTTGGACAC
TTTGAAGAAATTCTGCACGATAAATTGAAAGTGCAGGGAGCGAAAGCAGAACTGGCAATAG
TTCTCCTGCCTCGGTGGAGCGGGAGAAGACAGATGCTTACAAAGTCCTGAAAACAGAAATGAG
TCAGAGAGGAAGTGGACAGTGCCTTATTCAAGCAAAGGATTCGTTGGCATCAAATCT
AAGTTGTTTACAAAGATTGTTTTAGTACTAAGCTGCCTGGCAGTTGCATTTGAGCC
AAACAAAAATATTATTTCCCTCTAAGTAAAAAAA

166/168

FIGURE 166

MAAAPGLLFWLFWLGALWWVPGQSDLSHGRRFSDLKVCGDEECMLMYRGKALEDFTGPDCRF
VNFKKGDDVYVYYLAGGSLELWAGSVEHSFGYFPKDLIKVLHKYTEEELHIPADETDFVCFE
GGRDDFNSYNVEELLGSLELEDSPVEESKKAEEVSQHREKSPEESRGRELDPVPEPEAFRADS
EDGEGAFSESTEGLQGQPSAQESHPTHSGPAANAQGVQSSLDTFEEILHDKLKVPGSESRTGN
SSPASVEREKTDAYKVLKTEMSQRGSGQCVIHYSKGFRWHQNLSLFYKDCF

Important features of the protein:

Signal peptide:

amino acids 1-22

N-glycosylation site.

amino acids 294-298

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 30-34

Tyrosine kinase phosphorylation site.

amino acids 67-76

N-myristoylation sites.

amino acids 205-211, 225-231, 277-283

Amidation site.

amino acids 28-32

FIGURE 167

CCAGGACCAGGGCGCACCGGCTCAGCCTCTCACTTGTCAAGAGGCCGGGAAAGAGAAGCAAAGC
GCAACGGTGTGGTCAAAGCCGGGCTCTGCTCGCCTCTAGGACATACACGGGACCCCTAA
CTTCAGTCCCCAAACCGCGACCCCTCGAAGTCTGAACCTCCAGCCCCCACATCCACGCCGG
CACAGGCGCGGCAGGCAGGTCCCGCCGAAGGCAGTCGCGCAGGGGGTCGGGCAGCTGG
GCTCGGGCGGCAGGGAGTAGGGCCCGCAGGGAGGCAGGGAGGCTGCATATTCAAGAGTCGCCGG
CTGCCCTGGCAGAGGCCCTCGCTCCACGCAACACCTGCTGCTGCCACCGCGCCGC**A**
TGAGCCGCGTGGTCTCGCTGCTGGCGCCCGCCTGCTCTGCGGCCACGGAGCCTCTGCC
GCCCGTGGTCAGCGGCCAAAGGTGTGTTGCTGACTTCAGCATCCCTGCTACAAATGG
CCTACTTCCATGAACGTCCAGCGAGTGAGCTTCAGGAGGCACGCCCTGGCTTGAGAGTG
AGGGAGGAGTCCTCAGCCTGAGAATGAAGCAGAACAGAAAGTTAATAGAGAGCATGTTGC
AAAACCTGACAAAACCCGGGACAGGGATTCTGATGGTATTCTGGATAGGGCTTGGAGGA
ATGGAGATGGGCAAACATCTGGTGCCTGCCAGATCTTACCAAGTGGCTGATGGAAGCAATT
CCCAGTACCGAAACTGGTACACAGATGAACCTCCTGCCAGTGGAAAGTGAAGAAGTGTGATGT
ATCACCAACCAACTGCCAATCCTGGCCTGGGGTCCCTACCTTACCAAGTGGAAATGATGACA
GGTGTAACTGAAGCACAATTATATTGCAAGTATGAACCAGAGATTAAATCCAACAGCCCTG
TAGAAAAGCCTTATCTTACAAATCAACCAGGAGACACCCATCAGAATGTGGTTACTGAAG
CAGGTATAATTCCAATCTAATTATGTTTACCAACAATACCCCTGCTCTACTGATAC
TGGTTGCTTTGGAACCTGTTCCAGATGCTGCATAAAAGTAAAGGAAGAACAAAAC
GTCCAAACCAGTCTACACTGTGGATTCAAAGAGTACCAAGAAAAGAAAGTGGCATGGAAGT**A**
ATAACTCATTGACTTGGTCCAGAATTGTAAATTCTGGATCTGTATAAGGAATGGCATCAG
AAACAATAGCTTGGAAATGGCTGAAATCACAAAGGATCTGCAAGATGAACGTGAAAGCTCCCT
TGAGGCAAATATTAAAGTAATTCTTATATGCTTATTATTCAATTAAAGAATATGCTGTGCTA
ATAATGGAGTGAGACATGCTTATTGCTAAAGGATGCACCCAAACTCCTAAAGCAAA
TGAAATGGACAATGCAGATAAAGTGTATCAACACAGTCGGGAGTATGTGTTAGAAGCAAT
TCCTTTATTCTTCACTTCACTAAGTGTATCTAGTCATGTAATGTATATTGTATTGA
AATTTCAGTGTGAAAAGTATTTCACCTTGCATAAGTGTGTTGATAAAAATGAACGTGTTCTA
ATATTATTATTATGGCATCTCATTTCAATACATGCTCTTGATTAAAGAAACTTATTAC
TGTTGCAACTGAATTCACACACACAAATATAGTACCATAGAAAAAGTTGTTCTCGAA
ATAATTCACTTTCACTGCTTGGTCAATGCTAGGAAATCTCTCAGAAATAAGA
AGCTATTCAATTAAAGTGTGATATAACCTCCTCAAACATTACTTAGAGGCAAGGATTGTCT
AATTCAATTGTGCAAGACATGTGCTTATAATTATTAGCTTAAACAGATTGTT
TAATAATGTAACCTTGTAAATAGGTGCTAAACACTAATGCAATTGAAACAAAAGT
GACATACACAATATAAATCATATGCTTACACGTTGCCATATAATGAGAAGCAGCTCTG
AGGGTTCTGAAATCAATGTGGTCCCTCTTGCCCACTAAACAAAGATGGTTGTCGGGGTT
GGGATTGACACTGGAGGCAGATAGTTGCAAAGTTAGCTAAGGTTCCCTAGCTGTATTG
CTCTGACTATTAGTATACAAAGAGGTCAATGTGGTTGAGACCAGGTGAATAGTC
TGTGGAGACAAGCACAGCACAGACATTAGGAAGGAAAGGAACATGAAATCGTGTGAAA
ATGGGTTGGAAACCCATCAGTGATCGCATATTGATGAGGGTTGCTTGAGATAGAAAATG
GTGGCTCCTTCTGCTTATCTCTAGTTCTCAATGCTTACGCCCTGTTCTCAAGAGA
AAGTTGTAACCTCTGGTCTTCATATGTCCTGTGCTCCTTTAACCAAATAAGAGTTCTG
TTCTGGGGAAAAA

168/168

FIGURE 168

MSRVVSLLLGAALLCGHGAFCRVVSGQKVCADFHKPCYKMAFHELSSRVSFQEARLACES
EGGVLLSLENEAEQKLIESMLQNLTKPGTGISDGDFWIGLWRNGDGQTSGACPDLYQWSDGSN
SQYRNWYTDEPSCGSEKCVVMYHQPTANPGLGGPYLYQWNDDRCNMKHNYICKYEPEINPTAP
VEKPYLTNQPGDTHQNVVVTEAGIIPNLIYVVIPTIPLLLLILVAFGTCCFQMLHKSKGRTKT
SPNQSTLWISKSTRKESGMEV

Important features of the protein:

Signal peptide:

amino acids 1-21

Transmembrane domain:

amino acids 214-235

N-glycosylation sites.

amino acids 86-89, 255-258

cAMP- and cGMP-dependent protein kinase phosphorylation site.

amino acids 266-269

N-myristoylation sites.

amino acids 27-32, 66-71, 91-96, 93-98, 102-107, 109-114, 140-145, 212-217

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number
WO 01/16318 A3

(51) International Patent Classification ⁷ :	C12N 15/12. C07K 14/47, 14/705, G01N 33/53, C12N 15/62, C07K 16/18		PCT/US00/04414	22 February 2000 (22.02.2000)	US
(21) International Application Number:	PCT/US00/23328	PCT/US00/05601	1 March 2000 (01.03.2000)	US	
(22) International Filing Date:	24 August 2000 (24.08.2000)	60/187.202	3 March 2000 (03.03.2000)	US	
(25) Filing Language:	English	60/191.007	21 March 2000 (21.03.2000)	US	
(26) Publication Language:	English	PCT/US00/08439	30 March 2000 (30.03.2000)	US	
(30) Priority Data:	PCT/US99/20111	60/199.397	25 April 2000 (25.04.2000)	US	
	PCT/US99/21090	PCT/US00/14042	22 May 2000 (22.05.2000)	US	
		60/209.832	5 June 2000 (05.06.2000)	US	
(71) Applicant (for all designated States except US):	GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).				
(72) Inventors; and					
(75) Inventors/Applicants (for US only):	EATON, Dan, L. [US/US]; 75 Knight Drive, San Rafael, CA 94901 (US). FILVAROFF, Ellen [US/US]; 538 18th Avenue, San Francisco, CA 94121 (US). GERRITSEN, Mary, E. [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). GODOWSKI, Paul, J. [US/US]; 2627 Easton Drive, Burlingame, CA 94010 (US). GRIMALDI, Christopher, J. [US/US]; 1434 36th				

[Continued on next page]

(54) Title: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

<subunit 1 of 1, 266 aa, 1 stop
<MW: 29766, pi: 8.39, NX (S/T): 0
MWWFQQGLSFLPSALVIWTSAAFIFSYITAVTLHHIDPALPYISDTGTVAPEKCLFGAMLNIA
AVLCIATIYVRYKQVHALSPEENVIIKLNKAGLVLGILSCLGLSIVANFQKTTLFAAHVSGAV
LTFGMGSLYMFVQTILSYQMOPKIHGKQVFIRLLLVIWCGVSALSMLTCSSVLHSGNFGTDL
EQKLHWNPEDKGYVLHMITTAAEWSMSFSFFFLTYIRDFQKISLRVEANLHGLTLYDTAPC
PINNERTRLLSRDI

Important features:**Type II transmembrane domain:**

amino acids 13-33

Other Transmembrane domains:

amino acids 54-73, 94-113, 160-180, 122-141

N-myristoylation sites.

amino acids 57-63, 95-101, 99-105, 124-130, 183-189

WO 01/16318 A3

(57) Abstract: The present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.



Avenue: San Francisco, CA 94122 (US). **GURNEY, Austin, L.** [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). **WATANABE, Colin, K.** [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). **WOOD, William, L.** [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US).

(74) **Agents:** **KRESNAK, Mark, T.** et al.; Genentech, Inc., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *with (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description*

(88) **Date of publication of the international search report:**

29 November 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/23328

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C12N15/12	C07K14/47	C07K14/705	G01N33/53	C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 25825 A (BOUGUELERET LYDIE ;GENSET SA (FR); DUCLEERT AYMERIC (FR); DUMAS MIL) 27 May 1999 (1999-05-27) the whole document ---	1-20
X	WO 99 24836 A (ENDRESS GREGORY A ;HUMAN GENOME SCIENCES INC (US); FENG PING (US);) 20 May 1999 (1999-05-20) the whole document ---	1-20
A	EP 0 834 563 A (SMITHKLINE BEECHAM CORP) 8 April 1998 (1998-04-08) the whole document ---	
A	WO 97 07198 A (GENETICS INST) 27 February 1997 (1997-02-27) the whole document ---	
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

24 January 2001

Date of mailing of the international search report

23.04.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Smalt, R

INTERNATIONAL SEARCH REPORT

International Application No	PCT/US 00/23328
------------------------------	-----------------

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>YOKOYAMA-KOBAYASHI M ET AL: "A signal sequence detection system using secreted protease activity as an indicator" GENE, NL, ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, vol. 163, no. 2, 3 October 1995 (1995-10-03), pages 193-196, XP004041983 ISSN: 0378-1119 the whole document</p> <p>---</p>	
A	<p>KLEIN R D ET AL: "SELECTION FOR GENES ENCODING SECRETED PROTEINS AND RECEPTORS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, US, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 93, no. 14, 9 July 1996 (1996-07-09), pages 7108-7113, XP002061411 ISSN: 0027-8424 the whole document</p> <p>---</p>	
P,X, L	<p>WO 99 63088 A (BAKER KEVIN ;CHEN JIAN (US); GENENTECH INC (US); YUAN JEAN (US); G) 9 December 1999 (1999-12-09) L: priority. the whole document</p> <p>---</p>	1-20
P,X	<p>WO 99 46287 A (GENETICS INST) 16 September 1999 (1999-09-16) the whole document</p> <p>---</p>	1-20
E,L	<p>WO 00 73454 A (GENENTECH INC) 7 December 2000 (2000-12-07) the whole document</p> <p>-----</p>	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/23328

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 35-38, in as far as they pertain to in vivo methods, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-20 (all partially).

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 21-38 relate to a polypeptide, designated F or PRO1, which is not characterized in the description. This gives rise to a lack of clarity within the meaning of Article 6 PCT to such an extent as to render a meaningful search of the claims in respect of said protein impossible. Consequently, the search has been limited to the remaining parts of the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: 1-20, all partially

PRO180: nucleic acid with seq.ID.1, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.2 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.2 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide.

2. Claims: Inventions 2-76: claims 1-20, all partially

Subject matter as defined for invention 1, but related to the respective nucleic acid/polypeptide sequences of:

2. PRO218, represented by seq.ID.s 3 and 4,
3. PRO263, represented by seq.ID.s 5 and 6,
4. PRO295, as represented by seq.ID's 7 and 8,
5. PRO874, as represented by seq.ID's 9 and 10,
6. PRO300, as represented by seq.ID's 11 and 12,
7. PRO1864, as represented by seq.ID's 13 and 14,
8. PRO1282, as represented by seq.ID's 15 and 16,
9. PRO1063, as represented by seq.ID's 17 and 18,
10. PRO1773, as represented by seq.ID's 19 and 20,
11. PRO1013, as represented by seq.ID's 21 and 22,
12. PRO937, as represented by seq.ID's 23 and 24,
13. PRO842, as represented by seq.ID's 25 and 26,
14. PRO1180, as represented by seq.ID's 27 and 28,
15. PRO831, as represented by seq.ID's 29 and 30,
16. PRO1115, as represented by seq.ID's 31 and 32,
17. PRO1277, as represented by seq.ID's 33 and 34,
18. PRO1074, as represented by seq.ID's 35 and 36,
19. PRO1344, as represented by seq.ID's 37 and 38,
20. PRO1136, as represented by seq.ID's 39 and 40,
21. PRO1109, as represented by seq.ID's 41 and 42,
22. PRO1003, as represented by seq.ID's 43 and 44,
23. PRO1138, as represented by seq.ID's 45 and 46,
24. PRO994, as represented by seq.ID's 47 and 48,
25. PRO1069, as represented by seq.ID's 49 and 50,
26. PRO1411, as represented by seq.ID's 51 and 52,
27. PRO1129, as represented by seq.ID's 53 and 54,
28. PRO1027, as represented by seq.ID's 55 and 56,
29. PRO1106, as represented by seq.ID's 57 and 58,
30. PRO1291, as represented by seq.ID's 59 and 60,
31. PRO3573, as represented by seq.ID's 61 and 62,
32. PRO3566, as represented by seq.ID's 63 and 64,
33. PRO1098, as represented by seq.ID's 65 and 66,
34. PRO1158, as represented by seq.ID's 67 and 68,
35. PRO1124, as represented by seq.ID's 69 and 70,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

36.PRO1278, as represented by seq.ID's 71 and 72,
37.PRO1335, as represented by seq.ID's 73 and 74,
38.PRO1315, as represented by seq.ID's 75 and 76,
39.PRO1357, as represented by seq.ID's 77 and 78,
40.PRO1356, as represented by seq.ID's 79 and 80,
41.PRO1557, as represented by seq.ID's 81 and 82,
42.PRO1347, as represented by seq.ID's 83 and 84,
43.PRO1302, as represented by seq.ID's 85 and 86,
44.PRO1270, as represented by seq.ID's 87 and 88,

3. Claim : Invention

45.PRO1268, as represented by seq.ID's 89 and 90,
46.PRO1327, as represented by seq.ID's 91 and 92,
47.PRO1328, as represented by seq.ID's 93 and 94,
48.PRO1329, represented by seq.ID's 95 and 96,
49.PRO1340, as represented by seq.ID's 97 and 98,
50.PRO1342, as represented by seq.ID's 99 and 100,
51.PRO3579, as represented by seq.ID's 101 and 102,
52.PRO1472, as represented by seq.ID's 103 and 104,
53.PRO1461, as represented by seq.ID's 105 and 106,
54.PRO1568, as represented by seq.ID's 107 and 108,
55.PRO1753, as represented by seq.ID's 109 and 110,
56.PRO1570, as represented by seq.ID's 111 and 112,
57.PRO1446, as represented by seq.ID's 113 and 114,
58.PRO1565, as represented by seq.ID's 115 and 116,
59.PRO1572, as represented by seq.ID's 117 and 118,
60.PRO1573, as represented by seq.ID's 119 and 120,
61.PRO1550, as represented by seq.ID's 121 and 122,
62.PRO1693, as represented by seq.ID's 123 and 124,
63.PRO1566, as represented by seq.ID's 125 and 126,
64.PRO1774, as represented by seq.ID's 127 and 128,
65.PRO1928, as represented by seq.ID's 129 and 130,
66.PRO1865, as represented by seq.ID's 131 and 132,
67.PRO1925, as represented by seq.ID's 133 and 134,
68.PRO1926, as represented by seq.ID's 135 and 136,
69.PRO1801, as represented by seq.ID's 137 and 138,
70.PRO4405, as represented by seq.ID's 139 and 140,
71.PRO3435, as represented by seq.ID's 141 and 142,
72.PRO3543, as represented by seq.ID's 143 and 144,
73.PRO3443, as represented by seq.ID's 145 and 146,
74.PRO3442, as represented by seq.ID's 147 and 148,
75.PRO5990, as represented by seq.ID's 149 and 150, and
76.PRO4342, as represented by seq.ID's 151 and 152.

For the sake of conciseness, the first subject matter is explicitly defined, the subject matter of inventions 2-76 are defined by analogy thereto.

4. Claims: Invention 77: claims 1-3,5-12,14-38, all partially

PRO10272: nucleic acid with seq.ID.155, encoding a polypeptide comprising the amino acid sequence as

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

represented in seq.ID.156 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.156 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO10272 using its interaction with PRO5801 (seq.ID.158), method for linking a bioactive molecule to a cell expressing PRO10272 through the use of PRO5801, and method of modulating at least one activity of said cell thereby.

5. Claims: Invention 78: claims 1-3,5-12,14-38, all partially

PRO20110: nucleic acid with seq.ID.159, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.160 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.160 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO20110 using its interaction with PRO20040 (seq.ID.162), method for linking a bioactive molecule to a cell expressing PRO20110 through the use of PRO20040, and method of modulating at least one activity of said cell thereby.

6. Claims: Invention 79: claims 1-3,5-12,14-38, all partially

PRO10096: nucleic acid with seq.ID.153, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.154 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.154 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO10096 using its interaction with PRO20233 (seq.ID.164), method for linking a bioactive molecule to a cell expressing PRO10096 through the use of PRO20233, and method of modulating at least one activity of said cell thereby.

7. Claims: Invention 80: claims 1-3,5-12,14-38, all partially

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

PRO19670: nucleic acid with seq.ID.165, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.166 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.166 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO19670 using its interaction with PRO1890 (seq.ID.168), method for linking a bioactive molecule to a cell expressing PRO19670 through the use of PRO1890, and method of modulating at least one activity of said cell thereby.

8. Claims: Invention 81: claims 1-3,5-12,14-38, all partially

PRO5801: nucleic acid with seq.ID.157, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.158 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.158 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO5801 using its interaction with PRO10272 (seq.ID.156), method for linking a bioactive molecule to a cell expressing PRO5801 through the use of PRO10272, and method of modulating at least one activity of said cell thereby.

9. Claims: Invention 82: claims 1-3,5-12,14-38, all partially

PRO20040: nucleic acid with seq.ID.161, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.162 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.162 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO20040 using its interaction with PRO20110 (seq.ID.160), method for linking a bioactive molecule to a cell expressing PRO20040 through the use of PRO20110, and method of modulating at least one activity of said cell thereby.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: Invention 83: claims 1-3,5-12,14-38, all partially

PRO20233: nucleic acid with seq.ID.163, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.164 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.164 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO20233 using its interaction with PRO10096 (seq.ID.154), method for linking a bioactive molecule to a cell expressing PRO20233 through the use of PRO10096, and method of modulating at least one activity of said cell thereby.

11. Claims: Invention 84: claims 1-3,5-12,14-38, all partially

PRO1890: nucleic acid with seq.ID.167, encoding a polypeptide comprising the amino acid sequence as represented in seq.ID.168 or a nucleic acid having at least 80% homology thereto, vector comprising said nucleic acid, host cell comprising said vector, process for producing the protein of seq.ID.168 using said host, the isolated protein or one having at least 80% homology thereto, a chimeric protein of said peptide fused to a heterologous sequence, isolated extracellular domain of said protein or said protein lacking its signal peptide, and an antibody against said polypeptide. Also a method of detecting PRO1890 using its interaction with PRO19679 (seq.ID.166), method for linking a bioactive molecule to a cell expressing PRO1890 through the use of PRO19679, and method of modulating at least one activity of said cell thereby.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/23328

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9925825 A	27-05-1999	AU 1049199 A EP 1029045 A AU 1503099 A EP 1037977 A WO 9931236 A AU 2294499 A EP 1053318 A WO 9940189 A		07-06-1999 23-08-2000 05-07-1999 27-09-2000 24-06-1999 23-08-1999 22-11-2000 12-08-1999
WO 9924836 A	20-05-1999	AU 1303799 A EP 1032838 A AU 1303199 A		31-05-1999 06-09-2000 31-05-1999
EP 0834563 A	08-04-1998	JP 10179178 A US 5824504 A		07-07-1998 20-10-1998
WO 9707198 A	27-02-1997	US 5707829 A AU 727480 B AU 6712396 A AU 727489 B AU 6768596 A CA 2227220 A CA 2229208 A EP 0839196 A EP 0851875 A JP 11510045 T US 6043344 A WO 9704097 A US 6074849 A US 5969093 A		13-01-1998 14-12-2000 18-02-1997 14-12-2000 12-03-1997 06-02-1997 27-02-1997 06-05-1998 08-07-1998 07-09-1999 28-03-2000 06-02-1997 13-06-2000 19-10-1999
WO 9963088 A	09-12-1999	AU 4328699 A AU 2212299 A WO 9935170 A		20-12-1999 26-07-1999 15-07-1999
WO 9946287 A	16-09-1999	AU 2997299 A EP 1062233 A		27-09-1999 27-12-2000
WO 0073454 A	07-12-2000	AU 1748200 A AU 1932000 A AU 2192800 A AU 2495200 A AU 2600800 A AU 3381600 A AU 3514400 A AU 4328699 A WO 0053753 A WO 0053755 A WO 0075327 A WO 0053757 A WO 0053758 A WO 0073445 A WO 0073348 A WO 0073452 A WO 0032221 A WO 0036102 A WO 0037640 A WO 0075316 A		19-06-2000 03-07-2000 12-07-2000 28-09-2000 28-09-2000 28-09-2000 28-09-2000 20-12-1999 14-09-2000 14-09-2000 14-12-2000 14-09-2000 14-09-2000 07-12-2000 07-12-2000 08-06-2000 22-06-2000 29-06-2000 14-12-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/23328

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0073454 A		AU 2883600 A	28-09-2000
		WO 0053756 A	14-09-2000
		WO 0078961 A	28-12-2000
		WO 0104311 A	18-01-2001
		AU 1749800 A	04-10-2000
		AU 1749900 A	12-07-2000
		AU 2399300 A	28-09-2000
		AU 3107000 A	19-06-2000
		WO 0105972 A	25-01-2001
		WO 0032778 A	08-06-2000
		WO 0055319 A	21-09-2000
		WO 0037638 A	29-06-2000
		WO 0105836 A	25-01-2001
		WO 0053751 A	14-09-2000
		WO 0077037 A	21-12-2000
		WO 0109327 A	08-02-2001
		WO 0075317 A	14-12-2000
		AU 5922999 A	03-04-2000
		WO 0118210 A	15-03-2001
		WO 0116318 A	08-03-2001
		WO 0119987 A	22-03-2001
		AU 6498499 A	03-04-2000
		WO 0119991 A	22-03-2001
		AU 2224800 A	28-09-2000
		AU 2596700 A	28-09-2000
		AU 3107700 A	28-09-2000
		WO 0053754 A	14-09-2000
		WO 0053750 A	14-09-2000
		AU 2474700 A	19-06-2000

